NCRP REPORT No. 64

INFLUENCE OF DOSE AND ITS DISTRIBUTION IN TIME ON DOSE-RESPONSE RELATIONSHIPS FOR LOW-LET RADIATIONS

NCRP

National Council on Radiation Protection and Measurements

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INFLUENCE OF DOSE AND ITS DISTRIBUTION IN TIME ON DOSE-RESPONSE RELATIONSHIPS FOR LOW-LET RADIATIONS

Recommendations of the
NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS

Issued April 1, 1980

National Council on Radiation Protection and Measurements
7910 WOODMONT AVENUE / WASHINGTON, D.C. 20014

Library of Congress Catalog Card Number 80-81304

International Standard Book Number 0-913392-48-0

Preface

The aim of this report is to examine, on the basis of the best radiobiological data available, the influence of the temporal distribution of dose and of dose magnitude on the genetic and carcinogenic effects of radiation exposure in animals and man. The analyses and recommendations presented in this report were developed by Scientific Committee 40 of the NCRP, which is charged with the responsibility for analysis and evaluation of radiobiological data relevant to radiation protection. The analyses and recommendations of Scientific Committee 40 are for general use and are considered specifically by Scientific Committee 1 on Basic Radiation Protection Criteria in the development of basic radiation protection criteria.

The Council has noted the adoption by the 15th General Conference of Weights and Measures of special names for some units of the Systeme International d'Unités (SI) used in the field of ionizing radiation. The gray (symbol Gy) has been adopted as the special name for the SI unit of *absorbed dose, absorbed dose index, kerma,* and *specific energy imparted.* The becquerel (symbol Bq) has been adopted as the special name for the SI unit of *activity* (of a radionuclide). One gray equals one joule per kilogram; and one becquerel is equal to one second to the power of minus one. Since the transition from the special units currently employed—rad and curie—to the new special names is expected to take some time, the Council has determined to continue, for the time being, the use of rad and curie. To convert from one set of units to the other, the following relationships pertain:

$$1 \text{ rad} = 0.01 \text{ J kg}^{-1} = 0.01 \text{ Gy}$$
$$1 \text{ curie} = 3.7 \times 10^{10} \text{s}^{-1} = 3.7 \times 10^{10} \text{ Bq (exactly)}$$

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The Council wishes to express its appreciation to the members and consultants for the time and effort devoted to the preparation of this report.

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1. Summary

Data relating to the influence of the magnitude and temporal distribution of dose on the biological effectiveness of low-linear energy transfer (LET)[1] radiation per unit absorbed dose have been reviewed and evaluated. Although studies on a wide spectrum of biological endpoints in a variety of species and experimental systems were included, the evaluation has focused on the hereditary and carcinogenic effects that might occur in man after exposure to low doses[2] and/or dose rates[2]. It is clear from the data obtained for all endpoints examined, from cell death to tumor induction, that a reduction in dose rate in general results in a reduced biological effect. There are insufficient data on dose-rate effects in man to allow confident judgments on resultant changes in health risks; and thus the cumulative experimental evidence in plant, animal, and cellular systems must be brought to bear in formulating these judgments.

The risk per unit dose of low-LET radiation for cell killing and the induction of chromosome aberrations, mutations, teratogenic effects, tumor formation, and shortening of life has been observed in experimental systems to depend consistently upon both the magnitude of the dose and its temporal distribution. In general, the dose-response curves for low-LET radiation for late and genetic effects increase in slope with increasing dose and dose rate. The response for tumorigenesis may pass through a maximum and turn downward after a single high-dose-rate exposure at doses above about 250–400 rads often attributed to cell killing. Although dose-response relationships differ from one biological effect to another, qualitatively the relationships are similar. Thus, linear interpolation between the naturally-occurring spontaneous incidence and the incidence observed following exposure at intermediate-to-high doses and dose rates generally overestimates

[1] Sparsely-ionizing x, gamma, or beta radiations, as opposed to the more densely-ionizing radiations such as neutron recoils or alpha particles.

[2] "low" and "high" doses of sparsely ionizing radiation are arbitrarily defined here as 0–20, and about 150–350 rads, respectively. Doses in between are referred to as "intermediate," and doses in excess of 350 rads are placed in the "ultra-high" category. "High" and "low" dose rates are defined here as > 5 rads min^{-1} and < 5 rads y^{-1}, respectively. Dose rates in between those extremes are termed "intermediate" (see Appendix A for more extended discussion).

the risk of low-LET radiation at low doses and low-dose rates. This observation has also been incorporated in reports by the ICRP (1977), NCRP (1975), and UNSCEAR (1977).

The existence of dose-rate effectiveness factors has long been recognized from clinical experience and from studies of both genetic and somatic effects in experimental animals. Specific analyses of the implications of dose rate for the estimation of genetic risks were presented by the BEIR (NAS, 1972, pp. 61–68) and UNSCEAR (1972, 1977) committees. It was concluded that low-LET radiation delivered at high-dose rates is 3 times as mutagenic per unit absorbed dose as it is at low-dose rates. This conclusion was based on experiments with mice. From the studies on somatic effects in animals, summarized in the present report, the effectiveness per unit dose of low-LET radiation for life shortening and cancer induction is also generally lower at low-dose rates than at high-dose rates. The effectiveness per unit dose of high-vs. low-dose-rate exposure ranges from a factor of about 2 to about 10. In other words, linear interpolation from high doses (150 to 350 rads) and dose rates (>5 rad min^{-1}) may overestimate the effects of either low doses (0–20 rads or less) or of any dose delivered at dose rates of the order of 5 rad y^{-1} or less by a factor of 2 to 10. This factor is referred to as the Dose Rate Effectiveness Factor, or DREF.

Although extensive data from human beings permit reasonable risk assessments to be made for exposures to intermediate to high doses of low-LET radiation, these data are not adequate to demonstrate conclusively that a dose rate effect either does or does not exist. The experimental evidence from many different biological effects, including mutagenesis and carcinogenesis, and for many species of plants and animals in support of a dose rate effect is so extensive, however, that it would be extraordinary if such dependence did not apply to the same endpoints in the human being as well.

Because of the complexity and wide spectrum of the tumorigenic responses to radiation in the experimental animal, however, there appears to be no rigorously-defensible approach to deriving satisfactory DREFs for the human being, for either single tumor types or for all tumors collectively. Thus, the NCRP is reluctant at this time to go beyond providing a range of factors within which a single factor for the total yield of tumors in man after exposure of the whole body probably would lie. The DREF range is 2 to 10, when the actual absorbed dose is 20 rads or less, or the dose rate is 5 rads per year or less.

The extensive evaluations in this report with respect to radiation risks are focused on, and largely limited to, the effect of dose rate and dose magnitude. They do not address in detail other specific uncer-

tainties (e.g., "plateau" length, relative versus absolute risk) that must be dealt with in the derivation of risk coefficients (amount of effect per unit absorbed dose, or the slope of the dose-response curve) from data obtained at high doses and dose rates. It is emphasized that the conclusions on the effect of dose magnitude and dose rate apply only to low-LET radiations.

2. Introduction

Since the late 1940s and early 1950s it has been postulated that there may be no threshold level of exposure to ionizing radiation below which risks of injury are entirely lacking (NCRP, 1954; ICRP, 1955). At the same time, however, it has been recognized that the risks of exposure at levels approaching natural background can be estimated at the present time only by interpolation between levels of effect observed at high doses and dose rates and spontaneous levels of the same effect. The assumption of a linear, no-threshold dose-response relationship has generally been considered to provide a conservative approach to risk estimation for low dose and dose rate exposure, because the effect per unit dose for low-LET radiations has usually been observed in biology and medicine to decrease with decreasing dose and dose rate.

The aim of this report is to assess the genetic and carcinogenic effects of exposure in man to low doses of low-LET radiation, and to high doses delivered either at low-dose rates or in small increments protracted in time. Such effects may be expected in theory and on a statistical basis to occur at doses and dose rates well below those that cause acute effects. The assessment of the effects is then used to examine the validity of estimating the risk to man by interpolation from levels of effects observed at high doses and dose rates, on the assumption of a linear no-threshold dose-response relationship. The influence of LET and other factors related to spatial distribution of dose is not considered in detail because it is to be the subject of a separate report.

To determine the probability of the existence of a dose-rate effect for genetic and carcinogenic effects in man, the present state of our knowledge of the effects of low-LET radiation at all levels of biological organization is reviewed. Radiobiological data for *in vitro* cell cultures and for plants, experimental animals, and human beings are evaluated in order to determine any generalizations that may apply to the influence of dose magnitude, dose rate, and dose protraction on the degree of effect. The evaluations thus entail the examination of data for a number of endpoints other than genetic and carcinogenic effects. This approach has been considered appropriate since it appears necessary to make as extensive a survey as possible of the available data

for dose-magnitude and dose-rate effects, especially in the light of the fact that data for human exposure are limited. To the degree that such effects are found to be ubiquitous, the confidence that such effects must apply also to the endpoints of most direct interest in man will be increased.

The biological effect from a given dose of low-LET radiation is usually very much dependent on the time rate of energy deposition or on the total elapsed time during exposure. As an example, the time frame for biological repair in relation to the exposure time is a major factor in determining the degree of biological effect. The biological target may change with time, in terms of metabolic or other factors. Thus, the susceptibility for tumor induction (and/or for expression of an "induced" tumor) changes with the age of the animal. The effect of dose fractionation (repeated exposure to fractions of the total dose, rather than the same total dose delivered at an essentially constant average dose rate) may be highly dependent on the size of fractions and the dose rate within each fraction.

Thus, while precise specification of time-related factors can be complicated, for pragmatic reasons simplification of terminology is necessary. Hence the term "dose rate" (usually expressed as the mean) will be used generally to refer to the temporal pattern of delivery of the total dose, independent of further detail on the precise pattern employed. The term "protraction" is reserved for exposure times constituting a significant or sizeable fraction of the life span, and which are known or believed to be long enough to permit age-dependent changes in the radiosensitivity of the target (e.g., changes in susceptibility to tumor induction or expression with age). The term "true dose-rate effect" will be reserved for those situations in which it is desired to specify selectively dose-rate phenomena known or believed not to have been influenced significantly by the additional factors important in protraction effects (e.g., may include effects of repair of sublethal or other sub-effect damage, but not of age of the biological target). The term "fractionation" will be used in the sense indicated above, although its relevance to the effects of dose rate in terms of an average, other than for repeated small (few rads or less each) fractions, is usually remote.

Data obtained on "simple" cellular systems are used extensively, because the wide range of doses and the relatively small limits of error allow one to derive some insights and to illustrate possible interrelationships among dose magnitude, dose rate, and protraction of dose. Specifically, the "$\alpha D + \beta D^2$" relationship is developed and used extensively throughout the report. This model is applicable to many data in "simple" systems and it is useful and convenient as a framework

for the discussion of dose and dose-rate interrelationships for more complicated endpoints in more complex species, even when the model is known definitely not to apply. Hence its frequent use here must not be equated to an endorsement of its universal validity or applicability.

The principal focus in man is on genetic and carcinogenic effects, which can be described as "non-threshold." These have also been termed "stochastic" effects, for which the probability of occurring, rather than the severity, is assumed to be a function of dose, without threshold (ICRP, 1977). Thus, these effects may be assumed to occur, rarely and on a statistical basis, at doses and dose rates below those at which acute effects would be seen. Evaluations are presented of the degree to which predictions of risk of these stochastic effects derived from linear interpolation from data at high doses and dose rates obtained in the human being may not reflect the risk of exposure at low doses and dose rates. It is evident that the words "threshold" and "no threshold effect," particularly in the context of mutagenesis and tumorigenesis, refer to the appearance of the effect or endpoint of interest in one or a few individual(s) in an (usually large) exposed population, or alternatively to the probability or "risk" of that endpoint occurring in an individual in a similar population so exposed.

The intent in the evaluations of radiobiological data on the influence of dose magnitude and dose rate in this report has been to avoid underestimation or overestimation. Thus, the results are intended to reflect realistic judgments. Conservatism, if deemed appropriate, can be introduced and reflected in possible applications to risk estimation.

The problems addressed in this report can be visualized in simplified fashion by reference to Figure 2.1 in which are shown schematically data points and possible dose-response curves, e.g., for carcinogenesis in man. The figure depicts a typical situation in which only a few (not always precise) data points for high doses and high-dose rates are available. Data in the low-dose region are often not sufficient, because of statistical and other limitations, to contribute to determining the shape of the dose-response curve in the low-dose regions. The problem is to estimate the shape of the overall curve and its slope at very low doses in order to infer what the effect (risk) may be in this region. One straightforward approach, often used, is to fit the data with a straight line such as that shown in the figure (curve B) by interpolating linearly between the high-dose data points and zero excess incidence at zero dose. Use of this procedure does not necessarily imply a judgment with respect to the true nature of the dose-response curve. It is often used as a relatively simple approach to obtain an "upper limit" estimate of risk at low doses. If its use were intended to represent the correct dose-response relationship, then it is implied that the effect per unit dose

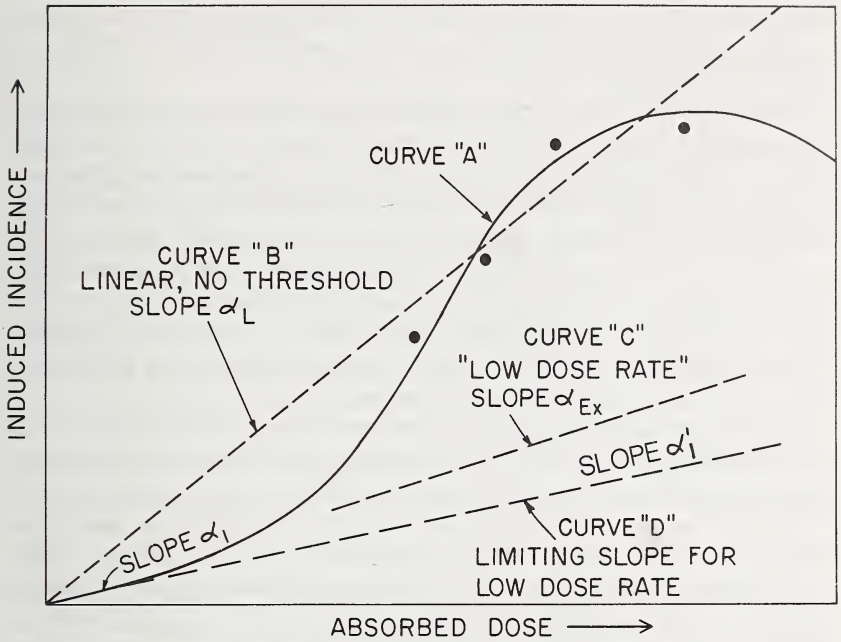

Fig. 2.1. Schematic curves of incidence vs. absorbed dose. The curved solid line for high absorbed doses and high dose rates (curve A) is the "true" curve. The linear, no threshold dashed line (curve B) was fitted to the 4 indicated "experimental" points and the origin. Slope α_1 indicates the essentially-linear portion of curve A at low doses. The dashed curve C, marked "low dose rate," slope α_{Ex}, represents experimental high-dose data obtained at low-dose rates. This experimental low-dose-rate curve may, in principle, at very low-dose rates, approach or become indistinguishable from the extension of the solid curve of slope α_1, the dashed curve D labeled "limiting slope for low dose rate."

(slope of the line, α_L, or risk coefficient) is independent of dose magnitude and that it would be expected to be independent of dose rate.

There are reasons that suggest, however, that a curvilinear relationship, curve A in Figure 2.1, is usually more appropriate. With a curvilinear relationship one would expect that cellular lesions producing a visible effect (e.g., a genetic defect, carcinogenesis) can result from the interaction of two or more sublesions. One would also expect repair of single sublesions, which are incapable singly of producing the effect. The maximal opportunity for sublesions to interact to form lesions would occur when the maximum number of sublesions is present in a given volume at a given time. This occurs when both the dose and the dose rate are high, i.e., large total numbers of sublesions

are produced per unit volume, and time is insufficient to allow repair to reduce significantly the number of sublesions available for interaction at a given time.

If the dose alone is progressively reduced (even if the dose rate remains high), then the total number of sublesions available for interaction is reduced with a consequent reduction in the number of lesions formed by the interaction of sublesions. Hence, lesions at low doses would have to be formed almost entirely by "single hit" kinetics, i.e., by radiation events capable singly of inducing the complete lesion. The resulting effect would be expected to be proportional to dose over this low-dose range.[3] Thus (Figure 2.1), the effect per unit absorbed dose at low doses would be expected to be equal to the slope α_1 of the low dose, relatively straight portion of the solid curve.

If, on the other hand, one progressively lowers the dose rate alone, even with high doses, the rate of buildup of sublesions is slower; and the time available, and thus the opportunity, for repair is progressively increased. Hence, fewer sublesions would be available per unit time and fewer lesions would be formed by their interaction. Thus, lesions at very low-dose rates also would be formed almost entirely by single radiation events, and the resulting effect would be expected to be proportional to dose. Thus, experimentally the effect per unit absorbed dose at low-dose rates and high doses would be expected to become progressively less as the dose rate is lowered. This would be manifest by the curvilinear solid curve A in Figure 2.1 becoming progressively more linear as the dose rate is reduced, depicted by curve C. In principle, the slope of this experimental curve would be expected, as the dose rate becomes very low, to coincide with curve D, slope α_1 (assumes complete repair of sublesions). This limiting low-dose-rate curve would be expected and appears to be an extension of the low-dose end of the solid curved line A (i.e., slope α_1' = slope α_1).

Hence, slope α_1 can be achieved in principle (and at least in some cases experimentally, as will be shown), either by reducing the dose to very low values independent of dose rate, or by reducing the dose rate to very low values independent of dose. The same slope α_1 is also attained in principle by high-dose exposure delivered in a series of "low dose" (less than about 5 rads) increments, and to this extent "highly fractionated" means the same as "low-dose rate."

In both cases, i.e., by lowering either the dose or the dose rate, the effect per unit absorbed dose (slope α_1 of curves A or D, or slope α_{Ex}) is less than the slope α_L obtained by simple linear interpolation using

[3] The above discussions have been oriented around the general model "$I = \alpha D + \beta D^{2}$" to describe the dose-response relationship. The model will be elaborated on in Section 3 in the context of actual data.

data at high doses and dose rates. It is a comparison of these slopes that yields a quantitative estimate of the degree to which linear interpolation or the "linear hypothesis" may overestimate the actual degree of effect at low doses and dose rates. In this report the ratio of the slope α_L of the linear no threshold linear fit to the high-dose and dose-rate data to slope α_{Ex} of the often apparently linear experimentally-determined curve for the low-dose rate data will be referred to as the dose-rate effectiveness factor, or DREF. As defined, the DREF will be greater than or equal to one.

The factor is termed a DREF even though it could be taken to be the ratio of α_L/α_1, i.e., a "dose-magnitude effectiveness factor." The term DREF is preferred, however, principally because it can be determined experimentally in mammalian systems in which statistical limitations effectively preclude the estimation of a dose-magnitude factor. Also, there are some data (see Sections 3, 6, 9, and 11) indicating that the two factors need not be identical, at least under some experimental conditions.

The data most directly useful for the derivation of DREFs for the endpoints most relevant to man (e.g., data on mutagenesis and carcinogenesis in other mammals) are limited largely to those obtained with relatively high doses, but different dose rates. Because of the experimental limitations, it is extremely difficult to detect radiation-induced effects in man and laboratory animals in the low-dose range at any dose rate, and thus only limited evaluation of the shape of the overall dose-response curve for high doses and dose rates has been achieved.

Numerical values of the DREF are derived, mainly at high values of dose and high- versus low-dose rates, although an analytical expression(s) could be devised from data on simple systems that would permit estimation of a DREF for any intermediate dose and dose rate. This degree of detail was not considered to be warranted by the data, however, since the constants for biological repair (and hence for dose-rate dependence) in different biological systems are not well known, nor are the "cell killing" functions in different systems (see the plateau and negative-slope high-dose region of curve A, Figure 2.1). Hence, only limited values of DREF, for the low-dose and dose-rate portions of the overall function, are provided.

An important consideration in calculating and applying the DREF is the confidence with which one actually knows the location of the "observed points" for a complicated function depicted as curve A in Figure 2.1. In animal systems one usually has adequate data on dose and dose rate such that the linear interpolation for the numerator does involve the region of the inflection point as the still-rising curve begins

to bend, and hence the DREF is for high doses and dose rates. For the usually limited human data from which a DREF might be derived, however, is the inflection point well enough known to avoid significant error? (If a DREF were based on "observed points" that actually lay substantially below or above the dose range of the inflection point, the value would be smaller than the maximum.) This potential problem appears to be more speculative than real. Some human data (developed in Section 10) do show inflection points, and these appear to occur at dose levels higher than seen in animals and lower systems. Also the human data, although inadequate to determine curve shapes at lower doses (less than 100–150 rads), do allow better definition at higher doses. With respect to dose rate, presumably this will be well enough known to render obvious the possible need for adjustment. Thus, the chance for serious error in these areas appears to be remote.

Of the several key factors that must enter into the overall quantitative evaluation of risk, only the DREF is dealt with definitively in this report. Perhaps equally important are several other factors involved in determining the high-dose and dose-rate coefficients to which the DREFs might be applied. These include: use of the relative risk versus absolute risk models (i.e., additional risk related to, vs. independent of the natural incidence); the latent period; the length of the "plateau" after exposure during which incidence may be increased above spontaneous incidence; the influence of other systematic and random variables (e.g., difference in susceptibility of different populations; effect of injurious agents other than radiation; combined effects of radiation and other agents). These variables are addressed in a number of other reports (NAS, 1972; UNSCEAR, 1972). The DREF can be applied independently of these other variables. For example, the BEIR Report (NAS, 1972) provides estimates of risk coefficients for high doses and dose rates, with assumptions stated for several of the variables mentioned here, including the assumption that effects are independent of dose rate. The DREF values provided here could, in principle, be applied to such estimates based on high doses of low-LET radiation delivered at high-dose rates to take into account the additional variable of dose rate.

3. Effects of Dose and Dose Rate in a "Simple" Biological System

The relationships demonstrated in the *Tradescantia* system examined below will be used as a framework in the later examination of more complicated and perhaps more relevant systems. No implication is intended that the relationships shown for the simpler systems necessarily apply, without modification, to complicated processes in higher systems.

A system that has proved to be extremely useful in radiobiology is *Tradescantia*, a common American garden plant (the spiderwort) having grasslike leaves and blue or purplish flowers. Its flower buds contain large numbers of "stamen hairs," each consisting of a chain of about 25 individual cells. Pink mutation events in the cells are readily inducible with a number of toxic agents, including radiation, and can be scored against the normal blue color. Hence, the extensive data necessary to evaluate mutation rates can be obtained more easily than in most other multicellular systems. The *Tradescantia* system has been chosen here for illustrative purposes[4] for the following reasons: 1) Effects (pink mutations) can be quantified[5] satisfactorily down to less than 0.3 rad of x-ray radiation and to considerably lower doses for higher-LET radiations. Hence, direct determination of effect is possible and no significant "extrapolation" to the very low-dose region is necessary. 2) The extent and range of precise quantitative data with respect to dose, dose rate, and radiation quality exceed those available for any other biological system. 3) Although the pink mutation in *Tradescantia* somatic cells has been shown to be the result of a macrolesion probably involving chromosome breakage and thus cytogenetic damage broadly related to genetic effects, the detailed mechanisms of radiobiological action at the molecular level are no more known or unknown than are those for a number of more complicated endpoints

[4] See Section 5 for an expanded discussion of radiation effects in *Tradescantia*.

[5] The Committee is indebted to Mr. Keith Thompson of the Biology Department, Brookhaven National Laboratory, for extensive statistical help with the analyses of the *Tradescantia* data.

in higher systems. Hence, even the most precise relationships developed in the simpler systems, as with all systems dealt with in the report, are empirical and are not based on a satisfactory understanding of the underlying basic radiobiological mechanisms involved. 4) The relationships between dose and/or dose rate that can be developed directly and accurately with the *Tradescantia* system appear to hold well, as will be seen, for a wide variety of effects directly observable in the individual cell in "simple" systems.

The basic *Tradescantia* data (Sparrow *et al.*, 1972; Nauman *et al.*, 1975; Underbrink *et al.*, 1976) for exposure to 250 kVp x rays are shown in Figure 3.1 on a full logarithmic plot for ease of data display over wide ranges of dose and effect. The curve can be separated into three regions. The region below about 10 or 15 rads is almost linear and of unit slope. If a threshold exists, it is much below 1 rad. The intermediate portion of the curve (about 10 rads to about 100 rads) is also essentially linear on the log plot, with a slope of 2, a value indicating a quadratic relationship. The data are, therefore, consistent with the linear-quadratic relationship, although other functions could be accommodated within limits of error of the data. The region of the curve beyond about 100 rads shows a flattening and then a decline that is consistent with an additional effect, such as cell killing[6], which prevents the manifestation of the pink mutation that presumably was "induced" by the exposure.

The data from Figure 3.1 are shown by the upper curve in Figure 3.2, which displays the simple linear plot commonly employed. Although the low-dose "linear portion" of the curve in Figure 3.1 can be envisioned, this region is now so "compressed" that no detail can be seen. The higher-dose portion of the curve (the only region available in the vast bulk of radiobiological experiments) is clear in the linear plot. The data depicted in Figures 3.1 and 3.2 illustrate a principal problem in dealing with data on mutagenesis, carcinogenesis, and life shortening in mammals. It is only in the intermediate-and high-dose regions displayed in Figure 3.2 that the majority of the data are available. The low-dose region depicted for *Tradescantia* in Figure 3.1 is largely inaccessible with the endpoints used in the more complicated systems because of statistical and experimental limitations. Hence, in the case of the more complex systems, possible quantitative relationships in the low-dose region can be inferred only through interpolation based on the high-dose region, and on models, hypotheses, or theories.

[6] Mutation rates are scored on the basis of surviving cells rather than cells at risk. This approach will affect the slope of the mutation dose-response curve (make it less steep) but the effect would not be expected to be significant in the dose range of 0–100 rads used principally here.

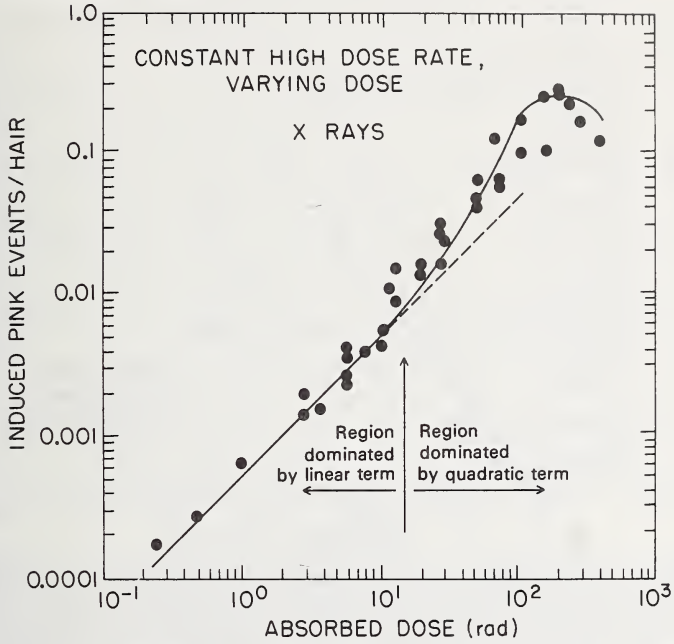

Fig. 3.1. X-ray dose-response curve for induced pink mutations in *Tradescantia*, on a log log plot to show detail in the low-dose range. The solid circles indicate experimental points at high-dose rate. Note that the low dose portion of the solid curve and its dashed-line extrapolation have a slope of unity corresponding to a linear, no threshold dose-effect relationship. The increased slope at higher doses indicates that the response involves a higher exponent of dose. See text for explanation of the linear "$\alpha_1 D$" and quadratic "$\alpha_1 D + \beta D^2$" portions of the curve (data of Sparrow *et al.*, 1972; Nauman *et al.*, 1975; Underbrink *et al.*, 1976).

The x-ray (250 kVp, moderately filtered) data in Figures 3.1 and 3.2 (ignoring for the moment the "cell killing" region) are represented by the equation,

$$I_x = 5.1 \times 10^{-4} D + 6.5 \times 10^{-6} D^2. \tag{3.1}$$

For gamma rays (^{60}Co), the coefficients are about 2.1×10^{-4} and 5.2×10^{-6}, respectively. The above data and the equation are a good example of the validity of the dose-response relationship

$$I_\gamma = \alpha D + \beta D^2, \tag{3.2}$$

in which I is the induced incidence, D is absorbed dose in rads, and the α and β terms are coefficients for the specific radiobiological conditions. The above relationship has been used extensively since the early days of radiobiology (e.g., Sax, 1941; Lea, 1955), and has been receiving

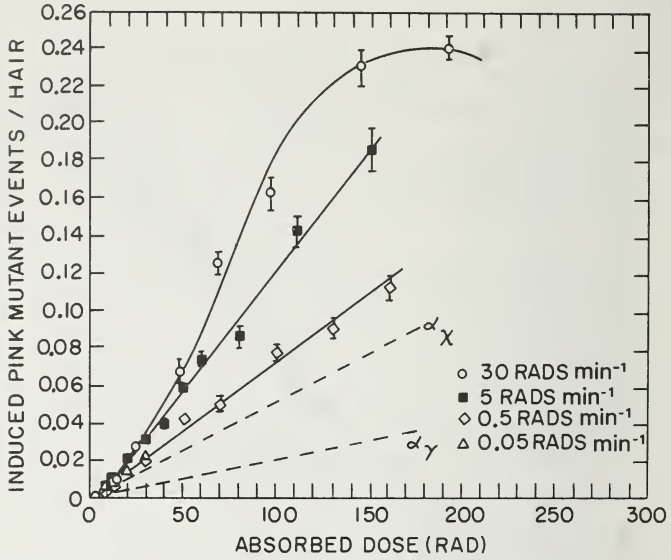

Fig. 3.2. Dose-response curves for pink mutant events/hair after x irradiation at 0.05 and 0.5 rad min^{-1} (combined in one line), and at 5 and 30 rad min^{-1}. The dashed lines represent the alpha terms in Equation (3.2) for x rays and gamma rays (From Nauman *et al.*, 1975).

greater acceptance with time. It has been shown to represent well a large amount of data in cellular systems up to about 300 rads (above 300 rads cell killing becomes dominant), and has proved to be quite useful as a general framework for discussion of possible dose-response relationships in a variety of circumstances.

Dose-rate effects have been studied extensively in *Tradescantia*, and the results of one experimental series are shown in Figure 3.2. The two lower (reduced dose rate) curves obviously have shallower slopes than does the upper (high-dose rate) curve, and correspond to curve C in Figure 2.1. At doses below 15 rads, all points appear to fall on the same straight line and the effect per rad shows no dependence on dose rate. At about 20 rads and above, a dose-rate effect is evident, i.e., at higher-dose rate, a deviation from linearity can be demonstrated.

It can be shown with the actual data that the slope of the lower solid curve in Figure 3.2 in fact becomes equal to that of the limiting slope α_1 in Figure 2.1. To demonstrate this, a *single* high dose of about 80 rads of ^{60}Co gamma rays was given and the dose rate was progressively lowered from about 500 rad min^{-1} to about 0.005 rad min^{-1} (exposure time increased from a small fraction of a minute to about 14 days). The results are shown in Figure 3.3, where the horizontal line corresponds to the effect at 80 rads for the linear or α term only in Equation (3.2), i.e., $I = \alpha D = 2.1 \times 10^{-4} \times 80$ rads $= 0.017$.

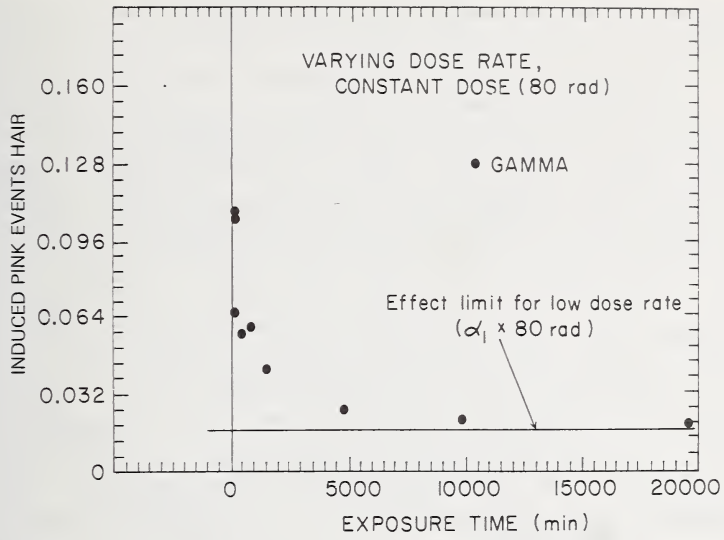

Fig. 3.3. Effect of dose rate on the effectiveness of a single large gamma-ray dose of about 80 rads for the induction of pink mutations in *Tradescantia*. The horizontal line represents the expected limiting low-dose-rate value for 80 rads [i.e., from the linear term for gamma rays of Equation (3.1), the value would be $2.1 \times 10^{-4} \times 80 = 0.017$]. Note that the effect at 80 rads decreases appreciably as the exposure time is increased and approaches asymptotically the limiting "αD" value for gamma radiation. (See text and Figure 2.1.)

As the dose rate is lowered progressively, the effect of 80 rads approaches the value expected if the limiting value of slope α_{Ex} in Figure 2.1 is slope α_1 in Figure 2.1.

The meaning of the situation described above can perhaps be visualized more easily by putting it in the framework of a mathematical model. The radiation acts as if it were made up of two separately-acting radiations, an "αD" component and a "βD^2" component (Figure 3.4). The αD component can be interpreted as "single hit," i.e., the interaction with the biological material is presumed to be "all or none" and the effect is presumed to be produced by one overall interaction that cannot be altered or reversed (see Section 6 for possible exceptions). The "βD^2" component, on the other hand, is "two-hit," i.e., two hits of this component are necessary at a sensitive site to produce the effect. Furthermore, since the potentiation from a single hit decays with time (this process is termed "recovery"), the second hit can produce the effect only if it occurs soon enough after the first. Thus, the probability of effective second hits increases with dose and with dose rate, and is negligible at sufficiently low doses and dose rates (even at higher doses), leaving only the αD component of the effect. Potentiated sites remaining at the end of an irradiation, of whatever

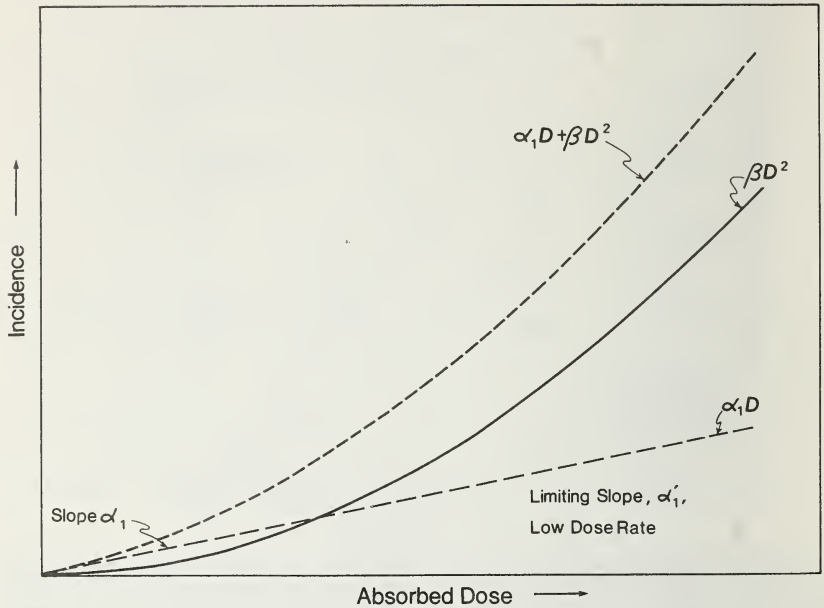

Fig. 3.4. The linear-quadratic dose-response curve for *Tradescantia*, with the linear and squared components plotted separately (high-dose region of curve dominated by cell killing is ignored for purposes of this plot).

dose and dose rate, will recover their original state in the absence of further radiation.

A further question, not yet specifically addressed experimentally in the *Tradescantia* studies, is the possibility of a dose-rate dependence of the slope of the low-dose essentially-linear ("$\alpha_1 D$") portion of the dose-response curve (see Section 6.5 for a discussion of such possible variation under some circumstances). That it is most unlikely that such a dependence could be shown experimentally is indicated by the overall regularity of the changes shown in Figures 3.2 and 3.3 as the total doses and dose rates are changed. As total doses in the 20 to 160 rad range were given at progressively lower-dose rates, the entire curve shifted downward in a regular fashion, approaching the slope of the $\alpha_1 D$ curve. At the single dose of 80 rads and with extensive dose-rate data, the location of the dose point approached the slope of the $\alpha_1 D$ curve asymptotically. Actual points on the low-dose $\alpha_1 D$ portion of the curve were obtained at dose rates as high as 30 rad min^{-1}, a dose rate at which the "βD^2" component is clearly dominant at high doses. Therefore, the slope of the $\alpha_1 D$ portion of the curve appears independent of dose rate. It would then follow that repeated low doses (less than 5–10 rads) or highly-fractionated exposure would be expected to

act essentially as low-dose-rate exposure, particularly if a period of days or more elapses between exposures. The slope of the dose-effect curve would be expected to approximate slope α_1 in Figure 2.1.

From the above data and discussion, and as shown in Figure 3.4, it is clear that most of the effect below about 100 rads may be considered as the sum of contributions of "linear" (αD) and "squared" (βD^2) components. The linear component contributes the same degree of effect per unit of absorbed dose at all doses, even very low doses. The "squared" component is seen only if the total dose and dose rate are high enough.

It should be recognized that not only can the ratio α/β in Equations 3.1 and 3.2 differ, but—and more importantly in the context of effect at low doses and dose rates—the absolute values of the slope α can differ substantially even among "low-LET" radiations that are essentially equi-effective at high-doses and dose rates (Bond, 1978, Bond *et al.*, 1978). The value of α_1 (250 kVp, moderately filtered; greater for lower energies) for x rays is about twice that for gamma rays (Bond, 1978; Bond *et al.*, 1978). Hence, the exact quality of the radiation can be important in evaluating the effects of "low-LET" radiations.

It is useful to evaluate the degree to which linear interpolation from high doses overestimates the effect at low doses and/or dose rates for the *Tradescantia* model. If the only data available are in the dose range of 100 or more rads, then linear interpolation between the data points on the upper curve in Figure 3.2 and zero excess effect yields a slope of about 17×10^{-4} rad^{-1} (analogous to curve B in Figure 2.1). The value of α_1 for this system is about 5.1×10^{-4} rad^{-1} for x rays. Thus, linear interpolation overestimates the effect per unit absorbed dose at low-dose rates by a factor of about 3.3.

The phenomenon of the dose-response curve leveling off and then falling at high doses (Figure 3.1) is seen frequently in radiobiology and specifically in curves for mutagenesis and carcinogenesis. Its cause, although incompletely understood, is frequently ascribed to cell killing. Since it is still seen in cell transformation experiments in tissue culture in which the results are normalized to surviving cells (see Section 6), it could be due at least in part to intracellular processes that prevent the presumed "induction" phenomenon from becoming manifest. Although dose-rate data are not sufficiently definitive, it is quite possible that the dose-rate dependencies of the "induction" and "killing" processes are different and that the flattening and decline would not be seen at high doses delivered at lower-dose rates. The "cell killing" phenomenon is an important consideration, particularly in regard to estimating the shape of dose-response curves for high-dose-rate exposure, and especially for the intermediate and high-dose regions. It has

been emphasized repeatedly that empirical observation of a linear dose-incidence relationship for radiation-induced cancer at doses of 100 rads or more must mean that the process of cancer induction itself cannot be truly linear, owing to the opposing effects of cell sterilization or other forms of damage at these high levels (Mayneord, 1978; Marshall and Groer, 1977; Mole, 1975a). On the other hand, the proliferation of tumor-forming cells may, under certain conditions, be promoted by the killing of other cells (Mayneord, 1978), the dose-incidence curve thus increasing in slope with increasing dose over a certain dose range.

The use of the linear quadratic formulation $I = \alpha D + \beta D^2$, derived empirically from extensive data in simple cell systems, is in agreement with models, hypotheses, and theories that have been used extensively for decades and that are currently considered to be applicable. Thus, even though there are substantial gaps in the knowledge of detailed mechanisms through which cellular effects are produced by radiation, there is remarkable agreement on at least descriptive dose-response relationships for cellular and sub-cellular effects. Intuitively, one might expect the dose-response relationship to be linear in those situations in which the biological effect is caused by a single charged particle traversal of a sensitive target, whereas the dose-response relationship might be expected to assume a quadratic or higher power function of the dose where two or more traversals are required. The well-known target theory incorporates this concept in the multi-hit or multi-target formulations. A low-dose linear component of the curve has been directly demonstrated above by using a biological system that permits examination in the low-dose range (see Sections 2, 3, and 5); and the model has been extensively used recently for both genetic and somatic effects (Brown, 1976).

The formulation is in accord with the biophysical theory developed by Kellerer and Rossi (1972). These authors have observed that the relative biological effectiveness (RBE) of neutrons for different end-points varies inversely as the square root of the neutron dose over several decades of dose, a finding that has led them to postulate a general radiobiological mechanism. According to their hypothesis, the biological effect arises from the interaction of sublesions at two locations within a site in the cell nucleus. The yield of sublesions is assumed to be proportional to the mean value of the specific energy[7],

[7] The specific energy is the energy imparted to a mass in an energy deposition event divided by the mass of the site. For uniform irradiation of a group of equal masses a distribution of specific energies is obtained, the mean value of which is the absorbed dose.

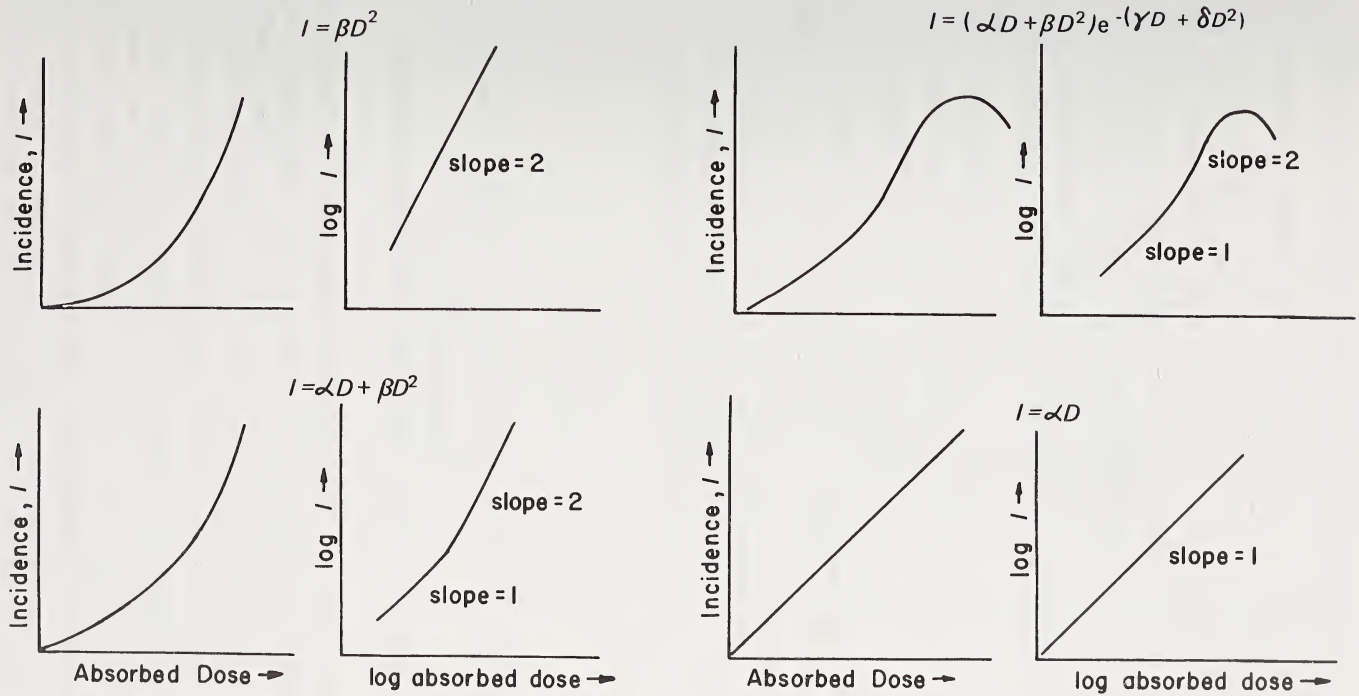

Fig. 3.5. Four different types of dose-incidence curves, linear and full logarithmic. The equation for each is also shown (integer values for slopes are approximations since a single overall function is described with contributions from terms having different exponents).

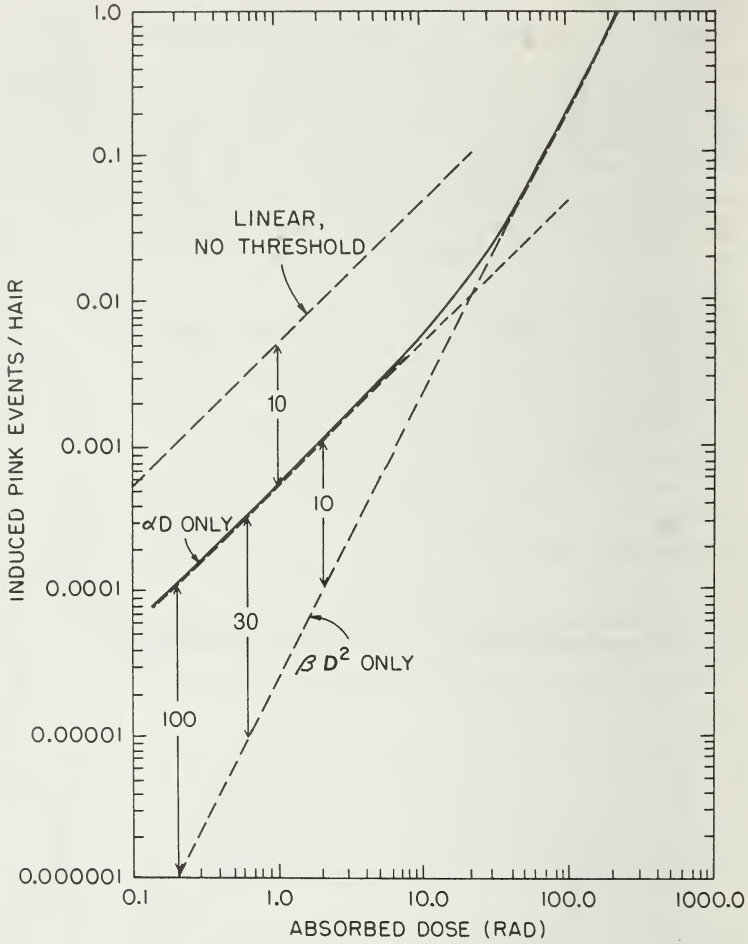

Fig. 3.6. Quantitative relationships among models, at low doses.

and the frequency of effect is therefore proportional to the square of the specific energy. Although the theory is more encompassing, it can be shown that the formulation, $I = \alpha D + \beta D^2$, is consistent with it. The coefficient of the linear term is a function of the quality (ionization density per unit mass or volume) of the radiation and the size of the site, and for high-LET radiation it is large. On the other hand, the linear term coefficient for "low LET" radiation is relatively small and assumes major importance only at low values of absorbed dose, while the quadratic term dominates at higher doses. The coefficient of the squared term is assumed to be approximately the same for all radiations and it is expected to approach zero if the absorbed dose rate is low and the cell is capable of complete repair of sublesions.

The parameter α/β has been used in relation to dose and dose-rate effects (Brown, 1976). It is the dose at which the linear and quadratic terms contribute equally to the total effect (i.e., the dose at which $I/2 = \alpha D = \beta D^2$, and $D = \alpha/\beta$). The significance of this value is that, if linear interpolation is performed from data obtained at doses near or below the value of α/β, then the resulting fit (Figure 2.1) might be expected to be a good estimate of the risk at low-doses and dose rates. If the interpolation is performed from data well above the value of α/β, then the linear interpolation may substantially overestimate the degree of risk at low-doses and dose rates. The parameter is not used in relation to the purposes of this report, for reasons given in Sections 9 and 11.

The models referred to above, i.e., the linear and the $\alpha D + \beta D^2$ formulations, are shown schematically in Figure 3.5. Also shown is a third formulation, the pure "dose squared" model.

In Figure 3.6 is shown quantitatively the relationship among these principal models at low doses. Note that the differences can be appreciable at "low doses" (5–10 rads) and that the difference between the "dose-squared" and the other models continues to increase substantially as the dose becomes lower. The same relationships would be expected to hold as the dose is held constant but the dose rate lowered, with the dose-squared model predicting zero effect at very low dose rates.

4. Genetic Effects

In this section those effects are considered that may be inherited through radiation-induced injury to the genes or chromosomes of germ cells. Also considered is relevant knowledge of the dose-response relationship for such effects as those derived from studies of the induction of mutations and chromosome abnormalities in somatic cells and in the cells of various experimental model systems.

The types of genetic changes considered include changes in chromosome number and gross (microscopically detectable) changes in chromosome structure, the latter presumably forming a continuum with the submicroscopic changes called point mutations. Mutational changes themselves may represent a broad spectrum of alterations in the deoxyribonucleotide structure of the genes. At one end of the spectrum this change can be represented by a single nucleotide base substitution or a base addition or deletion. At the other end of the mutation spectrum is the complete deletion of the entire gene and/or adjacent genes. For higher organisms these submicroscopic changes are not further resolvable in many instances, and they are simply classified as "mutations." In studies with microorganisms, or in certain favorable systems of higher organisms, more precise resolution of the mutational types can be demonstrated. Genetic changes of the same types as those occurring in germ cells may be restricted to the somatic cells of the body. While such changes can have varying effects on the individual in which they occur, they are not transmissible to subsequent generations.

The relevance to man of the experimental studies described below results from the following factors: the genetic material is of the same chemical nature in all organisms and its arrangement in the form of chromosomes in animals and plants implies that the response to environmental agents such as radiation and mutagenic chemicals will be very similar. The genetically-determined disease burden of man is very large; approximately 10 percent of all live-born individuals in our population suffer from recognized serious genetic disorders (UNSCEAR, 1977, p. 429) which are manifest either at birth or during the lifetime of the individual. This fraction may be expected to increase as our detection and recognition techniques improve. While the precise contribution from natural background radiation to this mutationally

determined disease burden is unknown, it is possibly in the range of 0.5–1 percent of the total genetically determined diseases (UNSCEAR, 1977). Moreover, it should be understood that, while not all mutations are necessarily harmful, the majority are deemed to be so. Those mutations that cause the most serious disorders usually are eliminated from the population within one to a few generations because the carriers do not survive to reproduce. On the other hand, those mutations that cause less severe disorders are expected to persist and affect more individuals because the carriers survive and reproduce.

4.1 Chromosome Aberrations in Somatic Cells

Although the relationship between the frequency of chromosome abnormalities (changes in chromosome structure and/or number) and the dose of radiation is one of the most thoroughly studied biological effects of radiation, the medical significance of the abnormalities remains in doubt (see Section 4.1.3). Early studies with plant cells, summarized in reviews by Sax (1941), Giles (1954), and Lea (1955), lead to several basic generalizations about dose-response relationships that have since been shown to be applicable to the cells of human beings and other mammals (UNSCEAR, 1969; 1972). Considerations of the kinetics of chromosome lesion induction after exposures to low-LET radiation are highly relevant to the present discussion of dose rate and dose magnitude effects for several reasons. (1) Radiation-induced chromosome damage can be readily assessed in cultured peripheral blood lymphocytes from persons exposed to low-LET radiation down to an absorbed dose of 10–25 rads. Cytogenetic methodology provides a sensitive parameter for directly evaluating one type of radiation damage in man. (2) Numerous studies in mammalian test systems (Bajerska and Liniecki, 1975; Clemenger and Scott, 1973; Brewen and Gengozian, 1971) and in man (Buckton *et al.,* 1971 and Schmid *et al.,* 1974) have shown that the frequencies of chromosome lesions induced in lymphocytes *in vitro* are both qualitatively and quantitatively similar to lesions observed after *in vivo* exposures. Thus, it can be presumed that data obtained with carefully controlled *in vitro* irradiations of human cells will accurately reflect the effects of dose magnitude and dose rate on the induction of cytogenetic lesions in exposed persons. (3) Since highly quantitative data can be obtained from *in vitro* exposures of human cells, lesion induction in lymphocytes exposed to moderate to high doses of low-LET radiation can be compared with similar data obtained after exposures of more sensitive

plant cells to low doses to determine whether basic kinetics that apply in plant systems are predictive of effects in human cells. (4) Cytogenetic evaluations provide one means of indirectly assessing the long-term biological consequences of human radiation exposures, since populations of exposed persons can be monitored to determine whether there are correlations between the frequencies of somatic cells bearing persistent radiation-induced lesions and increased risk for developing neoplastic diseases; and to determine the relative risk of transmission of cytogenetic lesions to offspring.

Extensive reviews of cytogenetic lesion induction in several mammalian species including man are available (NAS, 1972; Bender, 1969; UNSCEAR, 1972, 1977). This report will focus primarily on recent literature regarding dose magnitude and dose rate effects from studies in human cells exposed to low-LET radiation.

4.1.1 *Classification of Lesions*

In human, mammalian, and plant cells exposed to ionizing radiation, several classes of chromosome aberrations are induced. Simple deletions are frequently believed to result from a break in a single chromosome, and are thus termed one-event lesions. Other classes of aberrations, asymmetrical and symmetrical exchanges, are postulated to involve the exchange of chromosome segments resulting from two or more chromosome breaks and are thus termed two-event lesions.

Numerous classical studies in lower species have shown that the induction of one-event lesions varies linearly with dose of irradiation and is dose rate independent (Catcheside *et al.,* 1946; Carlson, 1941). Similar one-event lesions are induced in chromosomes of human lymphocytes, although several studies have shown variability in the observed frequencies of deletions among cultures from different persons exposed *in vitro* to low-LET radiation (Vulpus *et al.,* 1976). This variability in the frequencies of deletions in irradiated cells, coupled with the fact that deletions may be observed in cultured cells that have not been exposed to radiation, has prompted suggestions that these classes of aberrations are not the most reliable indicators of radiation dose to human cells.

The induction of two-event lesions varies as a higher power of the dose of x or γ rays delivered at high doses and dose rates. The relationship between yield, I, of such aberrations and dose, D, of low-LET radiation has been expressed as

$$I = C + \alpha D + \beta D^2 \qquad (4.1)$$

where C is the spontaneous aberration frequency (Lea, 1955). Several

recent studies have demonstrated that this relationship accurately describes the kinetics of exchange induction in human lymphocytes (e.g., Brewen and Luippold, 1971; Lloyd *et al.,* 1975; Schmid *et al.,* 1972). In Equation (4.1) the α (linear) term defines the proportion of exchange aberrations induced by a single radiation event, whereas the β (square) term defines the proportion of lesions induced by two or more radiation events. Because of the possibility of restitution, the formation of two-event lesions is dependent not only on the spatial orientation of the chromosomes within the nucleus, but also on the temporal juxtaposition of radiation events. It thus follows that one-event lesions (defined by the alpha term) should predominate over two-event lesions (defined by the beta term) for low doses of low-LET radiation and for radiations delivered at very low dose rates. Of the various types of two-event lesions induced in irradiated cells, the dicentric chromosome is considered to be the most reliable indicator of exposure in human lymphocytes because this lesion can be easily and objectively scored, shows little variability among cultures exposed *in vitro,* and is an extremely rare event in human lymphocytes which have not been exposed to radiation [spontaneous frequency of dicentrics estimated to be approximately 1 in 4000 lymphocytes metaphases (Evans, 1970)].

4.1.2 *In Vitro Studies*

Relationship of Exchange Induction to Dose of Low-LET Radiation. In over a dozen studies, human whole blood has been irradiated at 37°C to determine the kinetics of lesion induction after exposures of lymphocytes to low-LET radiation. In most of these studies, exchange induction has been evaluated in cells exposed to γ- or x-ray doses ranging from 20 to 800 rads delivered at exposure rates of 50R min^{-1} or greater. An example of the relationship of rings and dicentrics to dose after acute irradiation of whole blood to x-ray doses of 50–400 rads is shown in Figure 4.1. The exchange data gave the best fit to the linear-quadratic model $I = \alpha D + \beta D^2$ with an α coefficient of 9.1×10^{-4}, and a β coefficient of 6.0×10^{-6}. Because so few dicentrics are induced in lymphocytes exposed to low doses of low-LET radiation, there have been few attempts to define the kinetics of lesion induction in human lymphocytes exposed to dose magnitudes less than 20 rads. However, two recent studies that involved the analyses of extensive numbers of cells have shown no deviation from the predicted quadratic response in human lymphocytes exposed to doses as low as 5 rads (Lloyd *et al.,* 1975; Vulpus *et al.,* 1976). Figure 4.2 shows the dose-response curve for human lymphocytes exposed to x-ray doses of 5–

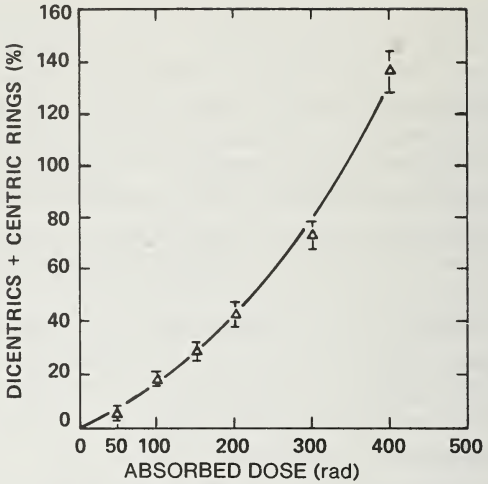

Fig. 4.1. Frequencies of rings and dicentrics induced in human lymphocytes after *in vitro* exposure to x-ray doses ranging from 50 to 400 rads delivered at an exposure rate of approximately 100 R min^{-1}. The data give a best-fit to the linear-quadratic model, $I = \alpha D + \beta D^2$ with $\alpha = 9.1 \times 10^{-4}$, and $\beta = 6.0 \times 10^{-6}$ (Redrawn from data from Brewen and Luippold, 1971).

800 rads. Based on these data the slope of the α component of the curve was calculated to be 4.76×10^{-4}, and that of the beta component 6.19×10^{-6}. In this study over 14,000 metaphases were scored to obtain quantitatively valid data at the 5-, 10-, 25-, and 50-rad dose points. The low-dose data are points shown on an expanded scale in the insert on the graph, along with the calculated slope of the α component. When these data are replotted on a logarithmic scale, the kinetics of dicentric induction in human lymphocytes (Figure 4.3) show close correlation with the kinetics of induction of pink mutant events in *Tradescantia* exposed to doses as low as a fraction of a rad (Figure 4.4). Based on the quadratic equation derived from the human data, it can be calculated that the dose of x radiation at which the α and β components contribute equally to dicentric induction (α/β) is 77 rads and that at a dose of 5 rads, virtually all lesions (94 percent) induced in human lymphocytes result from the linear component. The similarities in the kinetics of lesion induction in human and plant cells suggest that the slope of the alpha component derived from exposures of human cells to doses of greater than 5 rads would also be predictive of lesion induction in human cells exposed to lower doses.

In vitro cytogenetic studies in human lymphocytes also show close parallels with plant data in terms of relative effectiveness of x compared to γ radiation in very low-dose regions (see Section 5). Curves

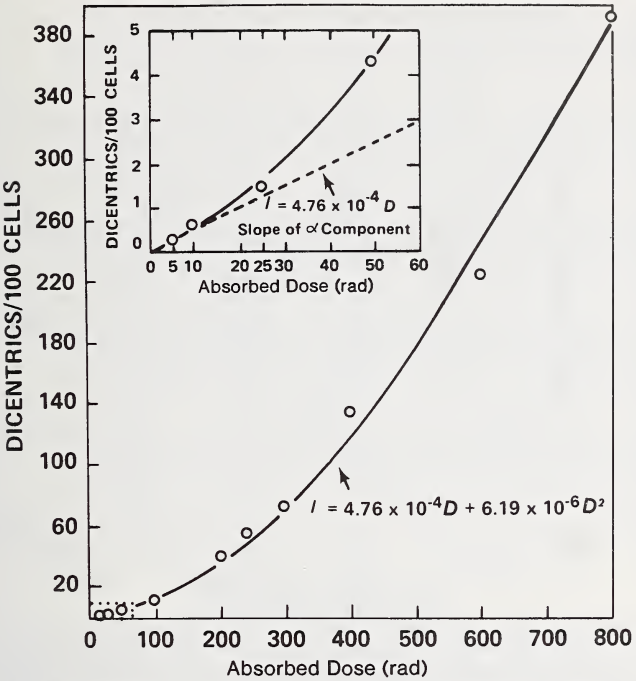

Fig. 4.2. Frequencies of dicentrics in human lymphocytes exposed to x-radiation doses ranging from 5–800 rads (250 kVp x rays, 100 R min^{-1}). Over 14,000 metaphases were scored to obtain data for the 5, 10, 25, and 50 rad points. Insert is an expanded graph showing data at low-dose points and the slope of the α coefficient (Redrawn from data from Lloyd *et al.,* 1975).

comparing dicentric induction in lymphocytes after acute exposures to the two radiations are shown in Figure 4.5. The coefficient of the α term for dicentric induction following acute exposure to x radiation is 4.8×10^{-4}, whereas the coefficient of the α term for γ radiation is 1.6×10^{-4}. Thus, in the human lymphocyte system, x radiation is shown to be approximately 3 times more effective in inducing dicentrics in the low-dose region than is gamma radiation. This factor of 3 difference in α terms generated from the human data for the two types of low-LET radiation shows excellent correlation with the factor of 2.5 derived in the plant system. Such similarities between human and plant cells in response to radiation further strengthen the premise that data on the basic kinetics of lesion induction obtained in simple plant systems will be generally predictive of cytogenetic effects in human cells.

Dose-Rate Effects in Human Lymphocytes. As is well established in other systems, evaluations in human lymphocytes irradiated *in vitro* have also shown that the frequency of dicentrics observed at specific

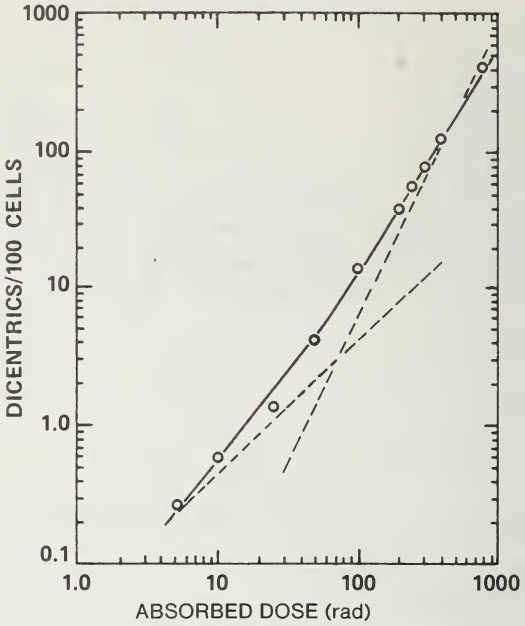

Fig. 4.3. Data from Figure 4.2 plotted on log scale. Solid lines represent best lines (by eye) to actual data points. Dashed lines are plots of the predicted slopes of the linear and dose square components derived from the equation $I = 4.76 \times 10^{-4}D + 6.19 \times 10^{-6}D^2$. From experimental data derived in this study $\alpha/\beta = 77$ rads and at a dose of 5 rads, 94 percent of the dicentrics are induced by the linear (α) component.

dose magnitudes will vary as a function of the dose rate at which radiation is administered (Brewen and Luippold, 1971; Lloyd *et al.,* 1975; Purrott and Reeder, 1976). An example of the effects of dose rate on dicentric induction is shown in Figure 4.6. As is shown in the figure, the observed yield of dicentrics at dose magnitudes of 250 and 500 rads is decreased by a factor of about 3 as the dose rate of ^{137}Cs gamma radiation is reduced from 400 to 10 rad h^{-1}. In a separate study comparing the effects of dose rate on lesion induction after exposure of human lymphocytes to ^{60}Co gamma radiation (Lloyd *et al.,* 1975), significant differences in the coefficient of the α term were not observed when the exposure rate was reduced from 3000 R h^{-1} to 18 R h^{-1}, whereas the coefficient of the β term decreased in value from $5.0 \pm 0.2 \times 10^{-6}$ to $2.91 \pm 0.47 \times 10^{-6}$ at the two exposure rates. These cytogenetic findings support classical theory that predicts that the α term in the quadratic equation (which in this instance predicts the number of dicentrics induced by a single ionizing track) is dose rate independent, whereas the β term (which predicts the number of dicentrics induced by two separate ionizing tracks) will decrease as the time between

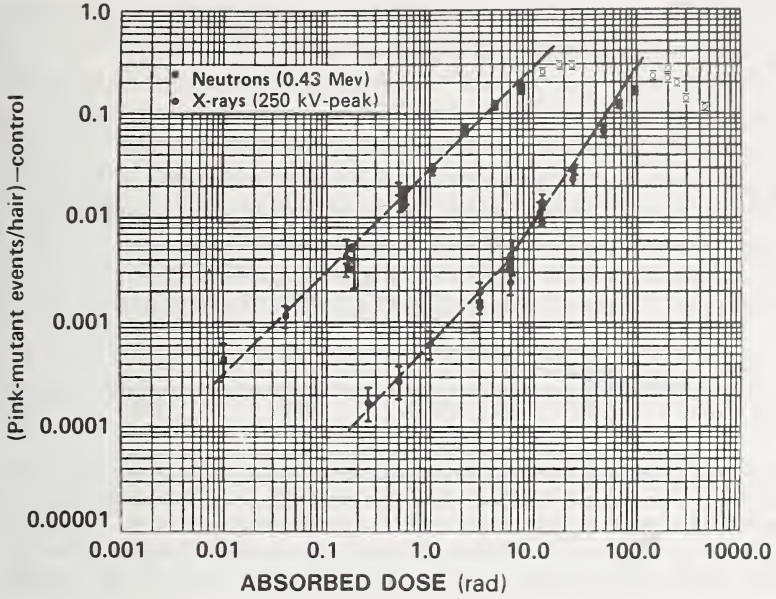

Fig. 4.4. Neutron and x-ray dose-response curves for pink-mutant events in stamen hairs of *Tradescantia* clone 02. The points represent average values obtained by dividing the total number of mutant events by the total number of stamen hairs scored from day 11 through day 15 after irradiation, when the mutation frequency is highest. The open symbols are saturation points and were not used in computing the true slopes. The dashed lines represent slopes based on computations (From Sparrow *et al.,* 1972).

successive ionizing tracks is increased. Thus, it might be speculated that at extremely low dose rates, the β term would become insignificant in terms of inducing exchange aberrations; and that all lesions would result from single tracks, which are described by the α term.

4.1.3 *Dose-Magnitude and Dose-Rate Effects In Vivo*

Although there are numerous reports of chromosome lesion induction in cultured lymphocytes from persons exposed to ionizing radiations (see Bender, 1969; UNSCEAR, 1969, for review), few studies have attempted to define the shape of the dose-response curve after human exposure to low doses of radiation. Two recent reports addressing this topic have yielded conflicting results. In one study, chromosome aberrations were evaluated in cultured lymphocytes from 122 persons working and living in the region of Badgastein in the Austrian Central Alps, an area having high background radioactivity (Pohl-Rüling *et al.,* 1978). These individuals received annual occupational or

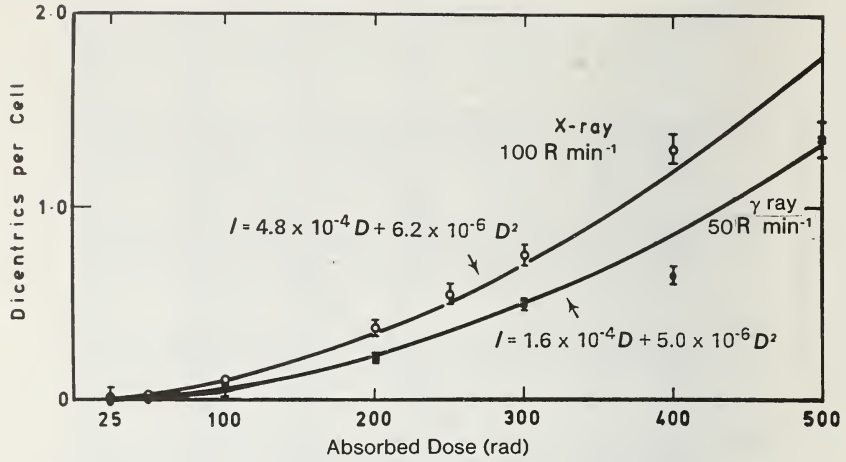

Fig. 4.5. Frequencies of dicentrics induced in human lymphocytes after *in vitro* exposure to x or gamma radiation. Note that relatively fewer lesions are induced by gamma radiation at all dose magnitudes. The initial differences in the two radiation curves can be attributed to differences in the linear component which is lower by a factor of about 3 for the gamma radiation (Redrawn from data from Lloyd *et al.*, 1975).

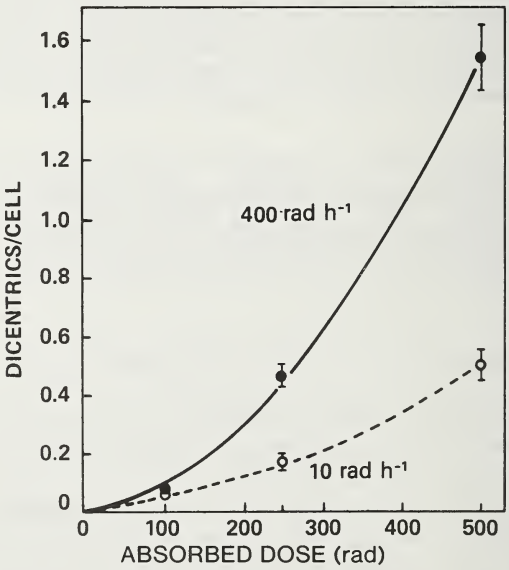

Fig. 4.6. Frequency of dicentrics induced in human lymphocytes exposed to cesium-137 gamma radiation delivered at 400 rads per hour (——) and 10 rads per hour (-----). At dose magnitudes of 250 and 500 rads, the low-dose rate yield of dicentrics is approximately one-third that observed at the high-dose rate (Redrawn from data of Purrott and Reeder, 1976).

environmental doses estimated to range from 0.8–260 mrads gamma and 0.8–1600 mrads alpha radiation from naturally occurring ^{222}Rn and its short-lived daughters. In this report, "blood doses" were estimated from measurements of environmental radioactivity in the living, sleeping, and working quarters of the individuals tested, taking into account the amount of time persons spent in various locations. When the sum of all chromosome breaks (deletions + dicentrics + minutes + rings) was plotted against estimated dose, the authors noted that the dose-effect curve rose sharply in the range of natural environmental radiation and subsequently flattened after about 300 mrads y^{-1} to produce

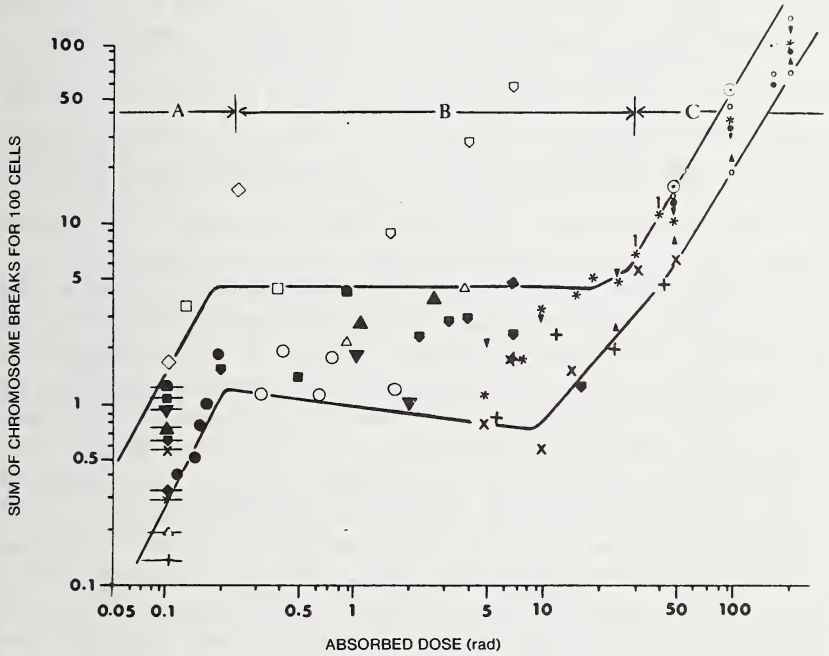

Fig. 4.7. Dose response curve for chromosome breaks in human lymphocytes compiled from data from several authors (From Pohl Rüling *et al.,* 1978). Chronic gamma burden; ● Continual, population in Badgastein, ◍ Continual population in Brazil, but with abruptly changing radiation field, Workers, Monazit ore mill, Bracin, ▲ Workers, Nuclear Industry, USA, ▼ Workers, Aeecre, Australia, ◖ Workers, UKAEA, UK, ◆ Workers, Radiation Center, Denmark. Chronic alpha burden: □ Continual ^{226}Ra burden, luminous dial painters, UK, ◇ Continual, ^{226}Ra burden, luminizing industry, Czechoslovakia, ▽ Continual, ^{232}Th burden, thorotrast patients, Austria, ○ Workers, thermal gallery, Badgastein, △ uranium miners, USA. Acute low-LET irradiation: ★ Patients, *in vivo,* partial body, USA, ◧ *in vivo,* accidental, whole body, ^{60}Co-gamma, USA, * *in vitro,* ^{60}Co-gamma, USSR, + *in vitro,* x rays, USA, × *in vitro,* x rays UK, ● *in vitro,* ^{60}Co-gamma, USA, ○ *in vitro,* x ray, USA, ⊙ *in vitro,* x ray, USA, ▽ *in vitro,* x ray, UK ▲ *in vitro,* ^{60}Co-gamma, UK.

a plateau. For comparison, the authors compared their findings with data published in several earlier reports and constructed a dose-response curve for chromosome lesion induction in human lymphocytes exposed to estimated doses of 0.1–100 rads (Figure 4.7). In compiling the graph, the authors note that for various reasons "the influence of time, kind, quality, and method of radiation" were not considered. Thus, the graph includes cytogenetic data from partial body and whole body, acute and chronic, and *in vivo* and *in vitro* exposures, to high- and low-LET radiations. From this information, it was concluded that: (1) the frequency of chromosome lesions rises sharply with dose at low-dose levels (range A, Figure 4.7); (2) at higher doses (range B) the effects plateau; and (3) only at doses above 30 rads are the dose-response kinetics described by the two component theory followed.

In sharp contrast, no deviation in chromosome lesion induction was observed at low doses in a second study of a population of British nuclear-dockyard workers (Evans *et al.,* 1979). Over a ten-year period radiation-induced chromosome lesions were evaluated in 436 lymphocyte cultures from 197 workers employed at an establishment for servicing and refueling nuclear powered submarines. Accumulated doses to the workers were determined from film badge exposures; and while the sources emitted mixed neutron and gamma radiation, the exposures were "almost exclusively gamma radiation." The types and frequencies of chromosome lesions observed in 43,715 lymphocyte metaphases from persons having mean total dose equivalents ranging from 0.2 to 41.3 rem are shown in Table 4.1 and Figure 4.8. Data were analyzed by multiple linear regression, assuming Poisson distributions, and taking into account the contributions of subject age at time of culture and date of sampling. From these analyses it was determined that: (1) the frequencies of dicentrics, acentrics, and cells with these unstable lesions are all consistent with a linear dose response, with no detectable second order effects of dose; (2) in all categories of exposed persons, a positive age-dose interaction was observed; (3) for all categories of exposed persons a greater (but not statistically significant) dose dependence was observed in cultures initiated within a few weeks after exposure than in cultures initiated a year or more after exposure. When dicentric induction was related to total dose equivalent received by the exposed group, a coefficient of $1.40 \pm 0.38 \times 10^{-4}$ dicentrics per cell rem^{-1} was calculated. This value is amazingly similar to the coefficient of the alpha term (i.e., $1.76 \pm 0.76 \times 10^{-4}$ dicentrics per cell rad^{-1}) derived from *in vitro* exposures of human lymphocytes to ^{60}Co gamma radiation delivered at an exposure rate of 18 R h^{-1} (Lloyd *et al.,* 1975). The data of Evans *et al.* (1979) provide strong evidence that

TABLE 4.1—*Frequencies of chromosome abnormalities in cultured lymphocytes from nuclear-dockyard workers.*[a]

Dose equivalent range (rem)	0.0–0.9	1.0–4.9	5.0–9.9	10.0–14.9	15.0–19.9	20.0–24.9	25.0–29.9	≥30.0	Total
No. of cultures[b]	87	85	91	91	36	29	11	6	436
No. of individuals[c]	80	80	71	68	29	22	9	6	197
Total cells examined	8,700	8,500	9,200	9,075	3,700	2,900	1,040	600	43,715
Mean age (y)	32.6	31.7	37.4	39.8	39.4	41.3	42.3	41..3	36.4
Mean dose (rem)	0.2	2.5	7.7	12.2	17.4	21.8	26.7	32.9	8.7
Mean date of culture	1971.9	1971.7	1972.1	1973.0	1973.8	1974.9	1975.0	1975.2	1972.6
Cells with additional or missing monocentrics (aneuploids)	219	247	317	305	105	98	24	13	1,328
Cells with abnormal monocentrics (Cs cells)	10	13	21	19	6	7	4	2	82
Cells with unstable aberrations (Cu cells)	26	40	50	62	30	22	11	8	249
No. of acentric elements	14	17	30	37	18	7	7	6	136
No. of dicentrics	14	23	21	32	21	15	6	2	134
No. of rings	2	6	5	4	0	3	1	0	21
No. of chromatid aberrations	156	200	199	224	73	63	30	21	966
Abnormal medium-sized (X?) Chromosomes	20	7	18	29	14	8	4	2	102

[a] Data from Evans *et al.* (1979).

[b] Few workers received as much as 5 rem y^{-1} so that more than one culture from an individual may occur within a given dose group.

[c] Approximately half of the individuals had two or more cultures analysed.

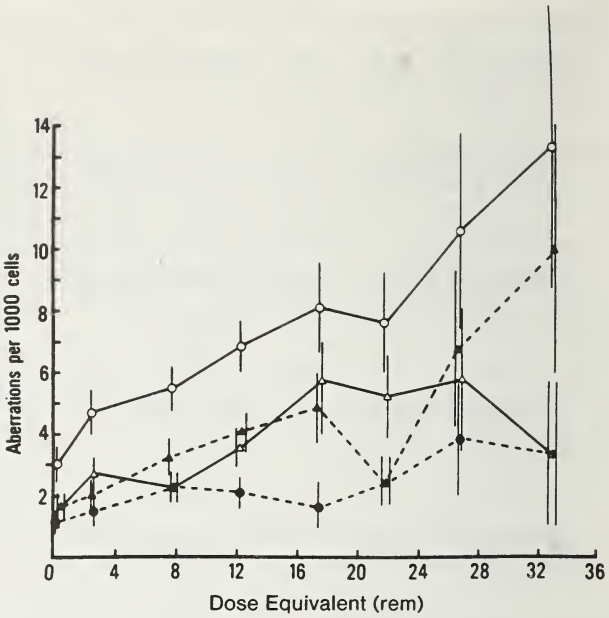

Fig. 4.8. Aberration frequencies (± S.E.M.) in cultured lymphocytes from nuclear-dockyard workers having accumulated dose equivalent of 0 – 36 rem. Dicentrics (△), acentric fragments (▲), cells with rings and dicentrics (○), cells with abnormal monocentrics (●). (From Evans *et al.,* 1979).

chromosome lesion induction in human lymphocytes is not aberrant at low doses when sufficient samples are evaluated from persons exposed to a specific quality of radiation.

There are little definitive data on the effects of dose rate on chromosome lesion induction in exposed persons. However, studies in experimental animals have verified that the induction of chromosome aberrations in somatic cells is also dependent on dose rate following *in vivo* exposures to low-LET radiation (Brooks *et al.,* 1969, 1971a). A curvilinear dose-response relationship has been observed for asymmetrical exchange induction in slowly dividing liver cells of Chinese hamsters after acute exposures to ^{60}Co gamma radiation delivered at high-dose rates (i.e., 5–15 rad min^{-1}) (Brooks *et al.,* 1971b). Reduction of the dose rate to 14, 44, 95, or 154 rad d^{-1} resulted in a concomitant decrease in these two-event lesions (Brooks, 1971a) as shown in Figure 4.9. For ring and dicentric induction in the Chinese hamster liver cells, a dose-rate effect was observed not only between the acute and chronic exposures to ^{60}Co gamma radiation, but also between chronic 6-day exposures and exposures of 15 days or more (Brooks *et al.,* 1971a).

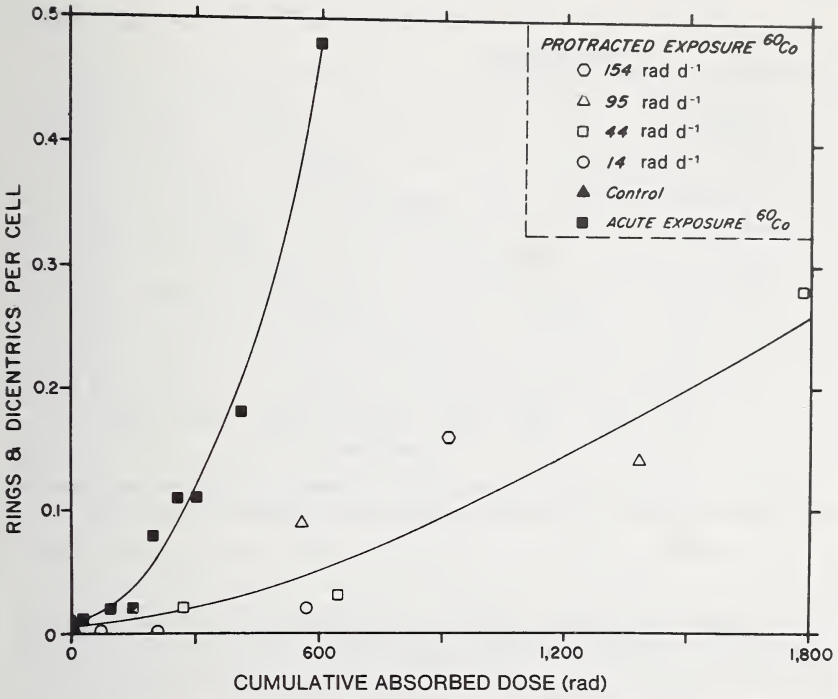

Fig. 4.9. Frequency of rings and dicentrics in Chinese hamster liver cells following acute (5–15 rad min^{-1}) or protracted *in vivo* exposures to ^{60}Co γ radiation (From Brooks *et al.,* 1971a).

4.1.4 *Biological Significance of Induced Cytogenetic Lesions*

Cytogenetic evaluations have been conducted for the purposes of dosimetry in persons having recent radiation exposures; and in many instances this method has proved valuable in providing biological estimates of dose (Brewen *et al.,* 1972; Dolphin *et al.,* 1973). Many other studies have been conducted in individuals exposed several years earlier, in attempts to determine the fate of somatic cells bearing lesions in irradiated persons.

In terms of numbers of persons examined, the largest follow-up study reported to date is that of the A-bomb survivors. In a recent comprehensive report of cytogenetic findings in 456 Hiroshima and Nagasaki survivors, Awa (1975) has reported that persistent radiation-induced lesions in cultured lymphocytes show reasonable correlations with estimated dose up to 25 years post-exposure (Figure 4.10). In the Hiroshima survivors the mode of increase in cells with exchanges was almost linear, whereas it appeared to be exponential in Nagasaki. Awa

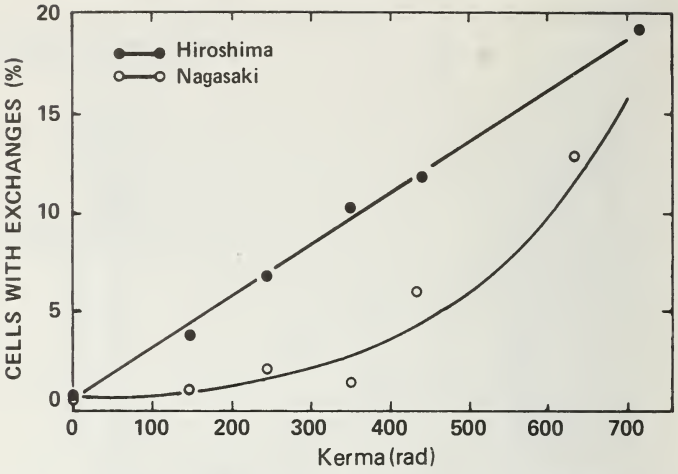

Fig. 4.10 Frequency of cells with exchanges in lymphocyte cultures from Hiroshima and Nagasaki A-bomb survivors 25 years after exposure (Data from Awa, 1975).

(1975) suggests that the difference between the two cities might be ascribable to differences in the radiation spectrum of the two bombs, since the ratio of neutrons to gamma was comparatively high in Hiroshima, while gamma rays contributed nearly all of the total dose in Nagasaki. In terms of the biological significance of the persistence of cells with radiation-induced lesions, Awa notes that no positive correlations of increased frequencies of chromosome lesions with any findings on past clinical evaluations have been observed. He concludes, "It may be said at this moment that the chromosome aberrations have not been associated with any past clinical manifestations in the heavily irradiated survivors." Whether such correlations will become evident longer than 25 years after exposure is not known.

In addition to studies of persistent lesions in lymphocytes, examinations of leukemic cells from exposed and non-exposed Japanese have shown that although cytogenetically aberrant malignant cell-lines were observed in both groups, no consistent abnormal patterns related to A-bomb irradiation could be detected (Kamada, 1969).

Extensive cytogenetic studies have also been conducted in the children of A-bomb survivors to determine the cytogenetic effects of irradiation on the germ cells of the parents (Awa, 1975). Evaluations in 2885 children born to exposed parents and 1090 children born to non-exposed parents showed no significant difference in the frequency of inherited chromosome lesions between the two groups.

4.1.5 *Summary of Cytogenetic Effects*

Cytogenetic evaluations in cultured lymphocytes from several species including man have shown no differences in the frequency of radiation-induced lesions in cells examined immediately following *in vitro* versus *in vivo* exposures. *In vitro* exposures of human lymphocytes to low-LET radiation have shown that: (1) the yield of two-track chromosome aberrations increases as a second order polynomial of the dose ($I = \alpha D + \beta D^2$), the squared term predominating at high doses and dose rates, the linear term predominating at low doses and dose rates; (2) x radiation is apparently more effective in inducing single-event lesions than is gamma radiation, a result that is reflected in the larger value for the α coefficient derived after *in vitro* exposures; (3) reductions in dose rate result in concomitant reductions in the frequency of two-event lesions. Significant differences in the coefficient α term have not been observed after reduction in exposure rate from 3000 to 18 R h^{-1}, whereas the β coefficient has been shown to be significantly lowered with comparable lowering of exposure rates. Long-term follow-up studies in heavily-irradiated persons have shown that lymphocytes bearing radiation-induced cytogenetic lesions persist for up to 25 years after exposure, and that the frequency of persistent lesions shows reasonable correlation with dose. To date, no clinical manifestations directly attributable to these lesions have been observed. Likewise, cytogenetic studies in children of exposed survivors and controls have shown no significant differences in the frequency of inherited chromosome lesions between the two groups.

4.2 Genetic Changes in Germ Cells

4.2.1 *Genetic Changes in Germ Cells*

Most information on the dose-response relationship for genetic effects in mammalian spermatogonia and oocytes—the principal germ cell stages that can be expected to accumulate dose as a result of their protracted, low-level irradiation of humans—comes from experiments involving gross chromosome aberrations and specific locus mutations in the mouse. These studies have been reviewed by UNSCEAR (1972, 1977). However, the emphasis is not the same as that presented in this report.

In addition, there is a wealth of data on a variety of non-mammalian animal germ cell stages that should have considerable bearing on the interpretation of the dose-response relationship. The UNSCEAR ref-

erences and a rather recent extensive review on radiation genetics in *Drosophila* (Sankaranarayanan and Sobels, 1976) are cited for their depth of coverage.

4.2.2 *Cytogenetic Studies*

Before introducing the relevant data on rearrangements induced in germ cells, it would be profitable to review the kinds of theoretical effects to be expected under varying dose regimens.

In Curve A of Figure 2.1 (the acute dose-response curve) there are four recognizable regions to which attention is now called. Region 1 represents the region where the linear component predominates; the quadratic or dose-squared contribution is small and becomes progressively smaller as the dose decreases. Within this region, neither different fractionation regimens nor dose-rate changes would be expected to influence the yield of induced events to any appreciable extent.

Region 2 represents the region where the dose-squared contribution is greatest. It is in this region that different dose-fractionation regimens will be able to influence the yield of induced events in a very significant manner. The larger the number of fractions employed, with sufficient interval between them to prevent interaction of effects (resulting from independent ionization or tracks), the smaller the yield of induced events relative to a single unfractionated dose. Low-dose-rate exposure should produce the minimum yield represented by the linear term.

Regions 3 and 4 represent the regions where saturation of effect is reached or where the curve indeed has bent over. In these regions, dose fractionation may induce more, the same, or fewer events than those observed by the single unfractionated dose depending upon the number of fractions employed and where on the curve the single dose yield is found.

Evidence for each of these expectations can be found in data to be presented in the following sections describing induced changes in germ cells. To illustrate this set of expectations, we provide Table 4.2 derived for the following conditions: $\alpha = 10^{-6}$; $\beta = 10^{-8}$; maximum yield before saturation occurs at 600 rads; the 800 rads observed yield is equivalent to the yield at 400 rads, i.e., it is in the descending region.

The results anticipated after different fractionation regimens, on the basis of the theoretical model, may be influenced in practice by biological or statistical factors. For example, while theory assumes that the biological material is static with respect to cell stage, radiation sensitivity, metabolic dynamics, etc., the fact that doses are applied with varying intervals between fractions frequently determines what

TABLE 4.2—*Theoretical yield of induced genetic events assuming* $I = 10^{-6}D + 10^{-8}D^2$ *with saturation at 600 rads*

Region of dose-response curve	Absorbed dose (rad)	No. fractions	Expected yield
1	50	1	7.5×10^{-5}
1	25	2	6.25×10^{-5}
1	10	5	5.50×10^{-5}
1	1	50	5.0×10^{-5}
2	400	1	2.0×10^{-3}
2	200	2	1.2×10^{-3}
2	100	4	0.8×10^{-3}
2	50	8	9.6×10^{-3}
2	8	50	0.43×10^{-3}
2	1	400	0.4×10^{-3}
3–4	800	1	$[7.2 \times 10^{-3}]$; (2×10^{-3})[a]
3–4	400	2	4.0×10^{-3}
3–4	200	4	2.4×10^{-3}
3–4	100	8	1.6×10^{-3}
3–4	25	32	1.0×10^{-3}
3–4	1	800	0.8×10^{-3}

[a] Observed because of saturation effect.

biological transition will be occurring over that time that can influence the induced yield relative to the theoretical expectations.

4.2.3 *Spermatogonial Studies in Mammals: Cytogenetic Effects*

With the advent of new cytological techniques, it became possible to study the effects of translocations induced in spermatogonial cells by subsequent examination of the spermatocyte stage. UNSCEAR (1977) provides an extensive review of the growing literature in this area. In the mouse, rabbit, and guinea pig, the dose-response curve is described by a linear-quadratic equation and may be distorted by high exposures that cause a saturation of effect occurring at about 500 R in cells of the mouse (Figure 4.11) and in the range of 200–300 R in cells of the other species.

From the studies of Preston and Brewen (1973, 1976), represented in Figure 4.11, a linear-quadratic fit was established for the data ranging from 50–500 R:

$$I = 1.08 \times 10^{-4}D + 5.0 \times 10^{-7}D^2 \tag{4.2}$$

The translocation yield of 17–19 percent shows saturation in the range of 500–600 R of single exposure; and at exposures above this, the familiar humped shape curve is obtained that indicates severe killing

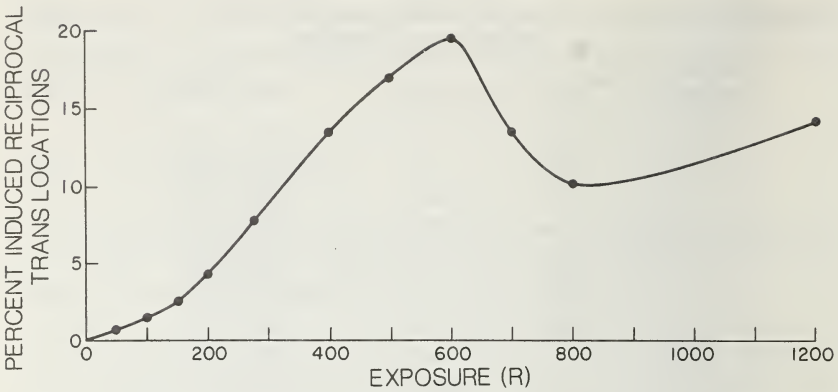

Fig. 4.11. Translocation dose response fitted to $I = 1.08 \times 10^{-4}D + 5 \times 10^{-7}D^2$ up to dose of about 500 R acute x rays unfractionated (data of Preston and Brewen, 1973).

TABLE 4.3—*Observed and theoretical frequency of translocations induced in mouse spermatogonia*

Exposure	Observed % yield ± 95% confidence limits	Predicted % yield[a]
300 R	6.3 ± 1.2%	6.2
5 × 60 R	3.4 ± 0.9%	2.6
30 × 10 R	1.3 ± 0.6%	1.9
60 × 5 R	1.7 ± 0.6%	1.8

[a] Fitted on the assumption that 60 × 5 R permitted calculation of the α coefficient and employing the β coefficient obtained by Preston and Brewen (1976) in the x-ray dose-response curve described in Section 4.2.6 on mutagenesis. Data of Lyon *et al.* (1970).

with associated selective elimination of the chromosomally damaged germ cells. Moreover, when seven repeated 400 R fractions separated by 8 week intervals were studied, the translocation yield increased additively from 13.8 percent for 400 R to 81 percent for 2800 R consistent with the theoretical expectations described in Section 4.2.2.

Clear evidence of dose fractionation effects has been found by other workers (Lyon *et al.*, 1970; Cattanach and Moseley, 1974). It is necessary to note that when a dose in the dose-squared region of the curve is applied in a fractionated fashion at intervals ranging up to 4 h, the yield is reduced to below that of the unfractionated dose. When the intervals between the fractions are longer than the time required to rejoin the breaks, the yields of translocations are, in general, equal to the sum of those resulting from the individual fractions, in agreement with theoretical expectations stated earlier. For example (Table 4.3),

when 300 R are acutely delivered as compared with 30 exposures of 10 R, or 60 exposures of 5 R, separated by daily intervals, the yield is reduced to about 25 percent of the yield after acute treatment; and for 5 exposures of 60 R, the yield is reduced to about 40 percent of the original yield.

The expected values fitted to the linear quadratic model

$$I = 5.7 \times 10^{-5} D + 10^{-7} D^2 \tag{4.3}$$

are shown in the last column of Table 4.3 in terms of percent and, in general, show good agreement with the data. Alternatively, Lyon *et al.* (1970) suggest that repeated irradiation made subsequent spermatogonial populations more radioresistant; such an *ad hoc* assumption is not required to explain the data. Note also that the α/β value which designates the inflection point in the linear quadratic response is approximately 100 rads for spermatogonia.

When the exposure rate is reduced, as in the studies of Pomerantzeva *et al.* (1972), the yield of translocations was linear for exposures ranging from 300–1200 R delivered at an exposure rate of 0.007 R min^{-1}. The yield was unchanged by further reduction to an exposure rate of 0.003 R min^{-1} (Pomerantzeva *et al.*, 1975). The equation fitted to the data was

$$I = 0.23 \times 10^{-2} + 1.74 \times 10^{-5} D \tag{4.4}$$

which is in excellent agreement with studies of Searle *et al.* (1968) and Brewen (1978).

The dose rate effectiveness factor for the lowest exposure employed, 300 R, was 4.4 and was chosen for illustrative purposes because it is well below the apparent maximum in the curve, i.e., 300 R at 710 R min^{-1} yielded 3.3 percent aberrations versus 0.75 percent when the exposure rate was 0.007 R min^{-1}.

More extensive work by Brewen *et al.* (1979) also shows a pronounced dose-rate effect, with the yield at the lowest exposure rate (0.0012 R min^{-1}) being 1.3×10^{-5} per R. While the yield per R declined over the entire range of exposure rates, the difference at the lower end of the exposure range was not significant, nor is there any reason to expect further reduction if it were feasible to lower the dose-rate. Finally, it should be noted that the data obtained by low-dose x-ray studies (250 kV x rays), when compared with low-dose rate gamma irradiation (^{60}Co), suggest that there may well be an RBE difference, with x rays being 2–3 times more effective.

4.2.4 *Studies on the Oocyte of Mammals: Cytogenetic Effects*

Brewen and his collaborators (Brewen *et al.*, 1976, 1977; Brewen, 1977; Brewen and Payne, 1979) have published data on the induction of chromosome aberrations in mouse oocytes, analyzed in metaphase *I*, that serve as a model indicator of the dose, dose-rate, and dose fractionation influence on response to x and γ irradiation.

The yield of chromatid aberrations, both exchanges and deletions, from oocytes recovered 9.5–28.5 days after irradiation (Table 4.4) was found to increase in a curvilinear fashion for acute x-ray treatment and was fitted to the equation I (interchanges) $= 5.1 \times 10^{-5} D + 3.2 \times 10^{-6} D^2$ and I (deletions) $= 11.4 \times 10^{-5} D + 2.6 \times 10^{-6} D^2$. With chronic gamma irradiations, the response over the same dose range is dramatically reduced and assumes a linear form I (interchanges) $= 8.5 \times 10^{-5} D$ and I (deletions) $= 12.1 \times 10^{-5} D$, respectively. The dose rate effectiveness factors range from about 20 at 400 R to about 4 at 100 R. The α/β values for oocyte rearrangements are 16 and 44, respectively.

With respect to fractionation effects, these workers have shown that exposures of 400 R split into 2 equal fractions show essentially complete interaction with respect to aberration yield when the interval between fractions is 90 minutes long; that is, essentially no repair has occurred within the interval. With an interfraction interval of 180 minutes, the yield is equal to the sum of two 200 R exposures, indicating that most of the damage introduced by the first dose had been repaired and was, therefore, unable to interact with that introduced by the second dose 180 minutes later. When the fractions were delivered as 100 + 300 or 300 + 100 R exposures separated by 90–180 minutes, the results were identical and in agreement with the important conclusion that the repair process is not inhibited by the radiation dose, since it might have been expected that the 300 + 100 R treatment would have required a longer time for additivity to be reached than the reverse dose procedure.

TABLE 4.4—*Pooled frequencies of chromatid aberrations in metaphase I oocytes (mouse) recovered 9.5–24.5 days after x-irradiation. Expected numbers determined from equation* $I = 0.22 \times 10^{-2} + 1.14 \times 10^{-4} D + 2.56 \times 10^{-6} D^2$ *for deletions;* $I = 5.14 \times 10^{-5} D + 3.24 \times 10^{-6} D^2$ *for exchanges.*[a]

Exposure (R)	Number of cells	Deletions observed	Deletions expected	Exchanges observed	Exchanges expected
0	500	1	—	0	—
50	666	10	10	7	7
100	978	43	38	42	37
200	854	95	108	104	119
300	1039	289	277	333	319

[a] Data of Brewen and Payne (1979).

In summary, the response of mammalian germ cells to low-LET radiation-induced chromosome damage is in all respects typical of other cytogenetic systems. Two hit lesions are induced by one or two energy deposition events, and they follow linear-quadratic kinetics for acute irradiation and linear kinetics for chronic exposures. Fractionation studies on oocytes indicate that most of the observed damage is repaired or rejoined between one and one-half to three hours (in a cell type which is not engaging in DNA synthesis except that involved in repair).

4.2.5 *Cytogenetic Studies in Germ Cells: Drosophila*

The early pioneering studies of Muller (1938; 1939a,b; 1940), Ray-Chaudhuri (1939; 1944), and Makhijani (1945) were unable to demonstrate any influence of dose rate on the yield of translocations in mature sperm of *Drosophila*. This result is now to be expected, however, since such germ cells are metabolically inactive. The yield of translocations in these cells with increasing dose has been demonstrated by many workers to follow a linear quadratic relationship or $D^{1.5}$ relationship (Belgovsky, 1937; Muller *et al.*, 1939; Timofeef-Ressovsky, 1939; Gonzalez, 1971a,b; 1972 whose studies were on exclusively male sperm and Shiomi, 1967 studying late spermatids).

Other kinds of induced rearrangements in male germ cells include dominant lethal damage (primarily resulting from chromosome breakage). From an extensive series of different studies, extending over a wide range of doses, Pontecorvo (1942), Eddington and Randolph (1958), Gonzalez (1971a,b) to name only a few workers, had been able to demonstrate that both a dose and a dose-squared contribution were required to adequately fit the data; for sex chromosome loss as well, Herskowitz *et al.* (1959) and Traut (1970) provide data with similar linear-quadratic components.

Herskowitz (1954) and Parker (1954) first demonstrated that chromosome rearrangements could be induced in female germ cells at appreciable frequencies and with a greater than linear dose response. The status of this area of research has been reviewed recently (Parker and Williamson, 1974).

The *maturing* oocytes of *Drosophila* (unlike the metabolically inactive mature stage 14 oocyte) are capable of undergoing restitution and rejoining of chromosome breakage within several hours. Herskowitz and Abrahamson (1956) demonstrated that the induced rearrangement frequency in these cell stages was dependent upon either dose-rate or dose-fractionation regimens. Reducing the dose rate or frac-

tionating the dose not only reduced the rearrangement frequency but as Abrahamson and Herskowitz (1957) demonstrated, these procedures simultaneously increased the fecundity of exposed females by decreasing the incidence of dominant lethality as measured by egg mortality studies (see also King *et al.*, 1956). Parker (1963), in reviewing his earlier studies (Parker and Hammond, 1958; Parker and McCrone, 1958) which independently demonstrated a linear-quadratic relationship for oocyte rearrangements, also showed that this applied to the mature stage 14 oocytes which are metabolically inactive (and are believed to require sperm entrance to iniate repair processes) and the less mature stage 7 oocytes which possess a rapid rejoining process. Abrahamson *et al.* (1971) extended Parker's dose-response curve over an exposure range of 10–500 R for stage 14 oocytes and demonstrated a dose-squared contribution above 50 R. Similar nonlinear dose-response kinetics, dose-rate, and fractionation effects in oocytes were demonstrated (Traut, 1964, 1968, 1971) for induced chromosome loss.

Few informative dose-response studies have been carried out on spermatogonial cells in *Drosophila* for induced rearrangements primarily because the yield is quite low.

4.2.6 *Mutagenesis*

> "When we conclude from an experiment that new genes have been evolved by the action of x rays, we are not simply stating the results of the experiment. We are, in a single statement, combining two distinct steps: (i) stating the observed results of the experiment and (ii) interpreting the mutations as due to a specific mechanism. It is essential that these two steps be kept separate, because the first step represents a permanent addition to the known body of fact, whereas the second step represents only an inference that may later be modified or contradicted by additional facts. When the two steps are unconsciously combined, we risk confusing what we know with what we only think we know.
>
> "The widely held belief that the frequency of gene mutation may be greatly accelerated by x-ray treatment was an illusion of this kind. Its basis was the use of the term *gene mutation* with two distinctly different meanings. Gene mutation was thought of as a change in the constitution of a unit of the genetic material, producing a new gene with altered gene action. Gene mutation was identified in experiments by the occurrence of a mutant character inherited as if it were due to a change in a gene.
>
> "The mischief involved in the use of the same term for the two concepts is obvious. To insist that x rays induce gene mutation because the mutants induced satisfy all the accepted criterions of

gene mutation, and that these mutants represent qualitative changes in specific genes because that is what we mean by gene mutation, is to adopt the dictum of Humpty Dumpty in *Through the Looking-Glass*. 'When I use a word,' Humpty Dumpty said, 'it means just what I choose it to mean—neither more nor less'."

The above quotation comes from a paper (published posthumously) of one of the giants in the field of genetics, L. J. Stadler, who independently discovered that x rays induce mutations (Stadler, 1954). These statements were chosen because they highlight the essence of one side of a major controversy that has existed in this field since its inception. On the other side of the issue was the other giant, H. J. Muller, who first demonstrated the genetic effects of irradiation and pioneered the development of the field with *Drosophila* experiments. The following quotations from a section of his paper (Muller, 1956) "On the Relation Between Chromosome Changes and Gene Mutations" attempt to extract the elements of his rebuttal and thus give balance to this ongoing dispute. However, it may well be the case for x-ray induced events that only nucleotide sequencing of the mutant genes or amino acid sequencing of their products will resolve this specific issue of whether intragenic mutations can be classified as single base changes or more complex losses or rearrangements of the genes studied.

"Does Radiation Produce Intragenic Mutations?

"The best answer we have to this question lies in the mass of data obtained in x- and gamma-ray experimentation on *Drosophila* which shows that despite the production of clear-cut deficiencies and other structural changes in a very large proportion of the seeming point mutations, and especially of those induced in stages with extended chromosomes, are in no known way distinguishable from the mutations that have arisen spontaneously. In fact, experience shows that every spontaneous mutant of *Drosophila* can, if thoroughly searched for, also be found after x-ray treatment. In the case of multiple-allele series, mutants of intermediate degrees of expression, including those deviating only slightly from the normal and those of more restricted rather than pleiotropic expression, as well as the more extreme and/or the more pleiotropic mutants, are produced by ionizing radiation, unlike what Stadler and his co-workers found in the case of the loci examined by him in maize. The same is true of partial and of complete reverse mutations, even though for most loci they are in both types of material much rarer than the abnormal mutations.

"It has been granted that in the case of any individual mutant,

> whether arising as a result of radiation or spontaneously, it is possible to construct a plausible hypothesis that will interpret it as an intergenic change, that is, as involving only a loss or duplication of a gene or genes and/or one or more position effects caused by intergenic rearrangement. Yet, if we accept the arguments previously given for the conclusion that, in addition to such phenomena, truly intragenic changes are included among the mutations which have arisen spontaneously in our laboratory and field material, then the above-mentioned extraordinary congruence between the bulk of our results on irradiated and on untreated *Drosophila* material leads us almost irresistibly towards the conclusion that the radiation mutations also include a considerable intragenic contingent."

H. J. Muller's forceful interpretation that x-ray induced intragenic mutations in germ cells of *Drosophila* were qualitatively distinct from cytogenetic aberrations and followed linear dose-response kinetics, had profound influence on his colleagues' and supporters' interpretation of their mutation studies.

Perhaps because plant material was involved, it was concluded by Muller that the difference in observations might reside in the source of the material rather than in the manner of action of x rays. The significance of these different interpretations should not be underestimated because the design and interpretation of experiments was greatly influenced by which view was supported by the particular investigator.

Within the context of this report, a framework has been provided for the vast array of biological data which deals with the problem of evaluating low dose, low-dose-rate, and dose-fractionation studies. The model developed, as discussed in previous sections, is that with increasing acute doses of irradiation the yield of events can be described by a linear-quadratic relationship. For low-dose rate and small fractionated doses, the quadratic term diminishes to zero leaving the residual linear term. While some workers in this area regard this model as too simplistic to account for gene mutations, there has been little disagreement for over thirty years that this paradigm adequately describes all of the cytogenetic data discussed in previous sections as well as that for rearrangements in germ cells of mammals and other organisms. It is believed that this dose-response model can be used to describe the results obtained in mutation studies. The mutation data have been analyzed in this manner because it is believed that the linear-quadratic construct provides a useful way of predicting responses to the questions at issue. Russell *et al.* (1958) and in subsequent references described below, have developed other models to explain the influence of dose, dose rate, etc. on the induced mutation yield but these more physio-

logical models lack the capability of predicting the experimental yields for the variety of radiation regimens studied at present.

4.2.7 *Male Germ Cells: Specific Locus Studies in the Mouse*

In acutely irradiated mice, the yield of mutations in spermatogonia appears to rise with exposures between 300 and 600 R and falls as the exposure is increased to 1000 R (Russell, 1956, as shown in Table 4.5, items 1, 2, and 6; and in Figures 4.12 and 4.13). Thus, these observations are very similar to those described for translocations induced over the same exposure range in these cells and suggest that the three exposures fall into regions 2, 3, and 4, respectively, of the theoretical curve described in Section 4.2.2. Based on these and other data described

TABLE 4.5—*X-ray induced mutation frequency in mouse spermatogonia for acute and fractionated doses based on seven specific loci*

Item[a]	Exposure	Mutants	Total F_1 offspring	Per locus mutation frequency ± 95% confidence limits × 10^{-5}
1	300 R	64	103755	8.8 ± 2.2
2	600 R	111	119326	13.3 ± 2.5
3	100 + 500 R 1 day interval	42	24811	24.2 ± 7.3
4	12 × 50 R 1 week intervals	16	18119	12.6 ± 6.2
5	60 × 10 R 1 day intervals	7	23982	4.2 ± 3.1
6	1000 R	29	44649	9.3 ± 3.4
7	2 × 500 R 2 h interval	12	14879	11.5 ± 6.5
8	2 × 500 R 7 day interval	11	8271	19.0 ± 11.2
9	2 × 500 R 4 day interval	11	7168	21.9 ± 12.9
10	2 × 500 R 1 day interval	55	16626	47.3 ± 12.5
11	5 × 200 R 1 day intervals	16	8588	26.6 ± 13.0
12	5 × 200 R 1 week intervals	15	10968	19.5 ± 9.9
13	600 + 400 R 15 week interval	10	4904	29.1 ± 18.0

[a] References:
Item 1 Russell (1963; 1968)
Item 2, 6, 7, 11, 12, 13 Russell (1963)
Item 3 Russell (1965b)
Item 4, 5 Lyon and Morris (1969)
Item 8, 9 Cattanach and Moseley (1974)
Item 10 Russell (1963); Lyon and Morris (1969).

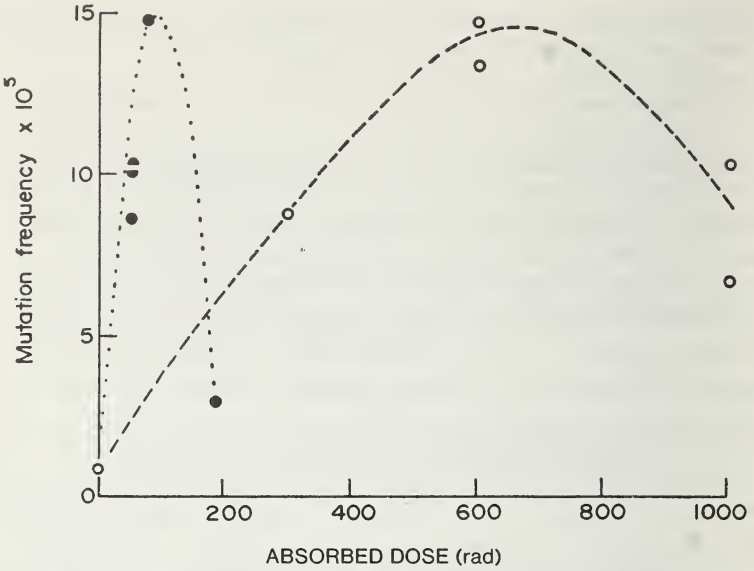

Fig. 4.12. Specific-locus mutation frequencies in mouse spermatogonia after fast neutron exposures of up to 12 hours (solid circles) and acute x-ray exposures (open circles). The γ ray components of the neutron doses have been omitted. The lines have been drawn by eye and are for guidance only. Note the falling off in yield at higher doses. Combined data from Batchelor *et al.* (1967), Phillips (1961), Russell (1963), and Russell (1965a).

below, a linear-quadratic per-locus fit was developed for acute spermatogonial irradiation (Abrahamson and Wolff, 1976):

$$I = 8.3 \times 10^{-6} + 0.69 \times 10^{-7}D + 0.66 \times 10^{-9}D^2 \qquad (4.5)$$

On fractionation, the mutagenic effectiveness of x irradiation per unit of absorbed dose may be *increased* or *decreased* depending on the *size* and *spacing* of successive exposures (Figure 4.13) relative to the unfractionated single exposure.

Table 4.5 contains all of the data for acute exposures of spermatogonia either from single or fractionated regimens. The data are presented as the per locus mutation rates with 95 percent confidence limits. As can be seen, the confidence limits are frequently very wide and can thus accommodate a variety of interpretations. The fractionated 1000 R exposures indicate that when the interval between the exposures is 2 hours (item 7) there is little change in the mutation frequency relative to the single 1000 R exposure (item 6). When, however, the interval is longer, 7 days or 4 days (items 8 and 9, respectively) the rate is increased. These combined fractionated groups are significantly higher as judged by the Fisher exact test ($P < .01$).

Item 10, the 24 h interval series is even greater than the single 1000 R series ($P < 5 \times 10^{-5}$) as well as items 8 and 9 ($P < .05$) and is statistically increased over the prediction of the linearly derived theoretical point. Thus, these results (similar to those for translocations) are again consistent with the expectation that fractionation of the exposure in region 4 will lead to increased yields relative to single unfractionated exposures. Items 11, 12, and 13 involve other fractionated regimens, 5 exposures of 200 R with 1 day or 1 week intervals and

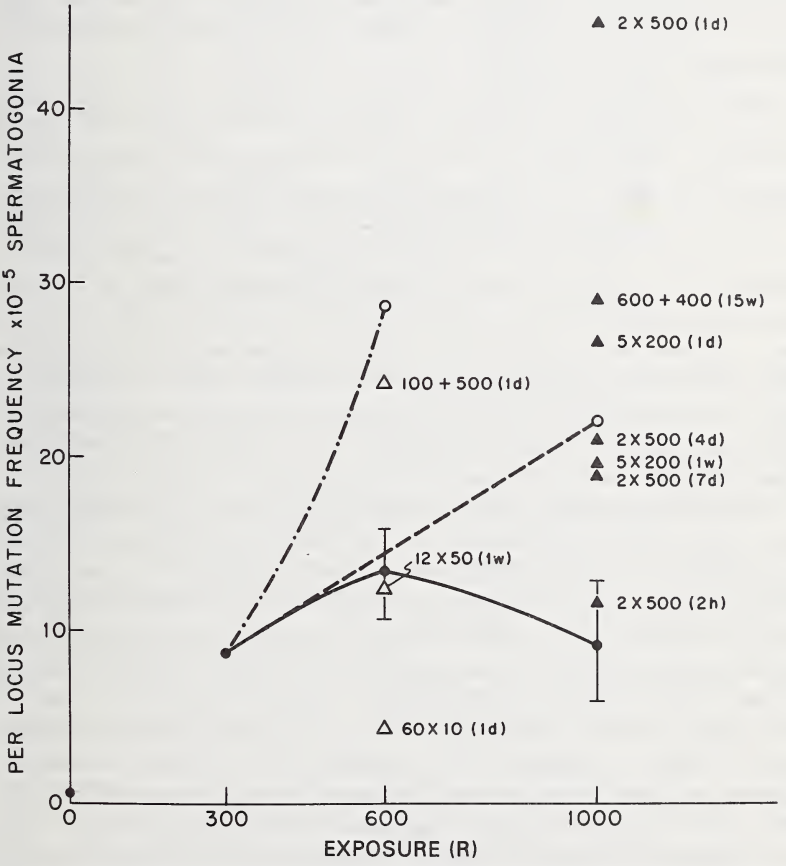

Fig. 4.13. Mutation rates at specific loci in mouse spermatogonia using pooled data of different workers as reviewed in Searle (1974) and Abrahamson and Wolff (1976); complete references with 95% confidence limits are given in Table 4.5. Solid circles for single acute exposures, open triangles for fractionated exposures totaling 600 R; solid triangle for fractionated exposures totaling 1000 R. The open circles represent theoretical yields by different models for single acute exposures.

600 R followed by 400 R with a 15 week interval, respectively. The observed yields are again consistent with the predictions based on Equation (4.5). The spermatogonial cell division time in mice is 8.6 days and these experiments may reflect the effect of the irradiation on different cell generations.

The data for fractionated 600 R exposures (presented in items 3, 4, and 5 in Table 4.5) indicate that a 1 day interval between a 100 and 500 R exposure increases the mutation rate significantly above the single 500 R exposure while 12 fractions of 50 R each separated by weekly intervals do not; and 10 R given in 60 fractions separated by 24 h each significantly reduces the mutation frequency below the single 600 R yield. These results are also in good agreement with the predictions of Equation (4.5).

Russell (1963) and Oakberg (1978) have argued that no appreciable selective elimination of mutant cells occurs at this exposure, 600 R. Oakberg's recent studies on survival of radioactively labeled spermatogonial cells show no evidence of selective elimination of cells at 600 R but do at 1000 R (UNSCEAR, 1977, Table 42). Interestingly, however, only 9 percent of the spermatogonial stem cells appears to survive an exposure of 600 R. For translocations there is evidence described earlier that the only other induced genetic effect that has been studied over a wide dose range in spermatogonia is showing saturation in the exposure range of 500–600 R. This, of course, does not prove that specific locus mutations will also show saturation in this dose range. It is again of interest to note that the α/β values for spermatogonia for both types of events are in the range of 100 R.

The mouse spermatogonial mutation studies are historically important and of major importance in that this system provided the first unambiguous demonstration of a dose-rate effect for mutational changes other than cytologically recognized gross chromosomal aberrations (Russell *et al.*, 1958). No dose-rate effects were demonstrable for mutations induced in mature sperm (a result consistent with the earlier observations in *Drosophila*). Mature sperm are devoid of cytoplasm and thus, although motile, are relatively inactive metabolically. There is, therefore, no opportunity for repair processes to operate and thus for dose-rate influences to occur in these cells. Unlike the mature sperm, the spermatogonial cells are metabolically active and, therefore, repair processes are capable of modifying the yield of mutations or chromosome aberrations when the dose is protracted.

On protraction of low-LET irradiation, the yield of mutations per rad in mouse spermatogonia decreases by a factor of about three as the dose rate is lowered from roughly 80–90 rad min^{-1} (Figure 4.13 and Table 4.5) to 0.8 rad min^{-1} (Figure 4.13, item 9 in Table 4.6). Further

TABLE 4.6—*The frequency of specific locus mutations induced in mouse spermatogonia at low-dose rates*

Item[a]	Exposure (R) and Source	Exposure rate (R min^{-1})	No. of mutants	Total F_1 offspring	per locus mutation rate ± 95% C.L. × 10^{-5}	Dose rate effectiveness factor
1	37.5 ^{60}Co	0.0011–0.0078	6	63,322	1.4 ± 1.1	
2	86 ^{137}Cs	0.001	6	59,810	1.4 ± 1.1	
3	300 ^{137}Cs	0.009	10	58,457	2.4 ± 1.5	
4	300 ^{137}Cs	0.0056	19	74,842	3.6 ± 1.6	
5	300 ^{137}Cs	0.001	15	49,569	4.3 ± 2.2	
6	300 ^{137}Cs	0.0007	11	42,020	3.7 ± 2.2	
∑3–6					3.5 ± 0.9	2.5
7	516 ^{137}Cs	0.009	5	25,325	2.8 ± 2.5	
8	600 X-ray	9.0 R min^{-1}	23	40,326	8.2 ± 3.3	
9	600 ^{137}Cs	0.8	10	28,059	5.1 ± 3.2	
10	618 ^{60}Cs	0.007–0.009	5	22,682	3.1 ± 2.8	
11	622 ^{60}Cs	0.005	20	58,795	4.9 ± 2.1	
12	600 ^{137}Cs	0.001	13	31,652	5.9 ± 3.2	
∑9–12					4.9 ± 1.4	2.7
13	861 ^{137}Cs	0.009	12	24,281	7.1 ± 4.0	

[a] References: Item 1, Carter (1958), Lyon *et al.* (1972b).
Item 2, 3, 5, 7, 8, 9, 12, 13 Russell (1963), Russell (1965a)
Item 4, 6 Russell and Kelly (1976)
Item 10 Lyon *et al.* (1972b)
Item 11 Batchelor *et al.* (1966), Lyon *et al.,* (1972b).

reduction of the dose rate to .009 rad min^{-1} fails to lower the yield proportionately. On the contrary, it has been suggested that the mutagenic effectiveness of the radiation may actually increase with further reduction in the dose rate (Lyon *et al.*, 1972a), but this interpretation rests on differences in mutation frequency that are not significantly different (UNSCEAR, 1972; Russell, 1974). Moreover, Russell and Kelly (1976) employed an exposure rate of 0.0007 R min^{-1} and obtained results consistent with the view that there is no significant change in mutation rate with decreasing dose rate below 0.8 R min^{-1}. The linear regression analysis for an extensive number of doses (Table 4.6) indicates that the α coefficient for mutation is 0.69×10^{-7} for gamma radiation. The issue of how effective dose protraction is in decreasing mutation yield relative to acute exposures is still in question, however, since the answer depends on establishing the true shape of the acute dose-response curve. This question, however, in no way affects estimates of genetic risk for protracted exposures to males.

The very clear demonstration that the mutation frequency is reduced by chronic irradiation is consistent with the finding that low dose fractionated exposure also results in reduced mutation frequencies relative to high dose acute exposure.

In summary, from the mouse spermatogonia studies it is clear that

chronic exposure reduces the mutation frequency below that observed for even the lowest acute exposure studied (300 R), as does the multiple low-dose fractionated exposure and these are the subjects of direct concern in this report. A final word of caution is required since the majority of the male studies were performed on young mice, the influence of age on mutation yield may have some impact on extrapolations to man. For the female, as will be shown below, age becomes an important parameter influencing mutation rates considerably.

4.2.8 *Female Germ Cells*

The interpretation of mutation induction in mouse oocytes is now quite complicated. As early as 1959 the possibility that the uniform dictyate oocytes in different stages of follicle development might give different mutational responses was recognized (Russell *et al.*, 1959). Data obtained since then have led to the recognition that a variety of morphological stages exist in the transition from resting oocyte to mature oocyte along with dramatic differences in their response to survival and mutation induction after irradiation. At present, it is not clear which stage in oocyte development might serve as a reliable model for extrapolation to estimate responses in the human ovary to irradiation, or which age of female mouse provides the appropriate data from which to extrapolate risk.

The very immature stages of the mouse oocytes, stages 1–3a (Oakberg, 1966), are remarkably susceptible to radiation induced killing. The LD 50 exposure is about 9 R, and 50 R destroys 99 percent of these cells (see review by Searle, 1974). When surviving cells from these stages are screened, usually seven or more weeks after irradiation, no mutations are recovered from either x-ray or neutron exposures (Russell, 1965c; 1972). In the former paper, Russell pointed out the importance of determining whether the result is due (a) to mutational insensitivity of oocytes in early follicle stages; (b) to an efficient repair mechanism in those stages; or (c) to cell selection. The *immature human oocytes*, in contrast to the mouse, appear to be considerably more resistant to killing. Recent studies on several rodent species (Cox and Lyon, 1975) failed to support the idea of an inverse relationship between oocyte killing and a measurable genetic effect (dominant lethality), however, since immature oocyte killing may not be reflected as dominant zygote lethality the question is still moot.

Much of the mutation rate data from the female mouse is that obtained from progeny conceived within 6–7 weeks post-irradiation, presumably derived from oocytes that were either mature or maturing (stages 3b–8) at the time of treatment. These oocytes generally give

rise to only 2 litters after acute irradiation. The mutation frequency for single acute doses deviates significantly from a simple linear response; Items, 1, 2, and 7 in Table 4.7. Lyon *et al.* (1979) report that for acute exposures of 200, 400 and 600 R to young females the dose-response curve is significantly different from linearity and may be fitted by linear-quadratic or quadratic relationships. These data have been interpreted differently by different authors (Russell *et al.*, 1958, Russell, 1967, Abrahamson and Wolff, 1976; Brewen and Payne, 1979). In view of the facts: that the oocyte stages sampled at the high dose (yielding first litters only) are not entirely equivalent to those at the lower doses (from which were produced both first and second litters); that the ages of the females used have not been well controlled; and that oocytes providing second litters from older females appear to be 2–4 times or more as mutable as those which give rise to the first litters (Searle and Beechey, 1974; Russell, 1977), it is perhaps not surprising that a variety of interpretations and uncertainties exists.

In Table 4.7 are also shown the data for fractionated exposures. At 400 R (Item 9, Russell, 1968a), 8 fractions of 50 R, each separated by 75 minute intervals, result in a significant reduction in mutation yield ($P < .01$ by Fisher exact test); whereas a treatment of two 200 R fractions, separated by a 24 hour interval (Item 10, Russell, 1965c), does not influence yield when compared to the single dose treatment (Item 7). This, however, is a small experiment with wide confidence limits. The age of the females and the distribution of mutants between the litters are as yet unreported. In experiments on young female mice by Lyon and Phillips (1975), 20 fractions of 10 R (Item 5), requiring either one week or one month (the data were pooled), very dramatically reduced the yield relative to a single unfractionated 200 R exposure (Item 4). Only 1 mutation was found in the fractionated treatments out of nearly 40,000 progeny examined for a per locus mutation frequency, which is a factor of 10 lower than that observed with the corresponding unfractionated treatment. The yield is in agreement with the predictions of Equation (4.6) (Item 5), however, it is not significantly greater than the per locus control value of 0.2×10^{-5} (Item 12).

With respect to low dose-rate exposures, protraction leads to significant reduction in mutation frequency (Table 4.7). An exposure of 400 R acute x ray (Item 7) delivered at 90 R min^{-1} results in approximately a four-fold larger mutation frequency as compared with an exposure rate of 0.8 R min^{-1} (Item 8a,b,c,), but clearly there is no difference when compared to second litters of older females (Item 8d). However, as Brewen and Payne (1979) point out, this may not be a legitimate comparison since the acute series only produced one litter.

TABLE 4.7—*Specific locus mutation frequencies in mature and maturing mouse oocytes under varying conditions of exposure, exposure rate, and fractionization*

Items[a]	Exposure and manner of delivery	No. of mutants	Total F_1 offspring	per locus mutation rate ± 95% C.L. × 10^{-5}	Dose rate effectiveness factor
1	50 R acute x ray (90 R min^{-1})				
	a. 1st litters (female mice ages unreported)	6	95,534	0.9 ± 0.7	
	b. 2nd litters	7	71,070	1.4 ± 1.0	
2.	200 R acute x ray (90 R min^{-1})				
	a. 1st litters (female mice ages mixed)	16	32,605	7.0 ± 3.4	
	b. 2nd litters (mostly old)	17	12,860	18.9 ± 9.0	
3	"207 R" effective dose chronic γ (0.009 R min^{-1} age unreported)	1	7,692	1.9 ± 3.6	5–∞
4	200 R acute x ray (55 R min^{-1} 9–10 weeks of age i.e., young female mice)				
	a. 1st litters	7	21,578	4.6 ± 3.4	
	b. 2nd litters	2	12,538	2.3 ± 3.2	
5	200 R (20 × 10 R[b] young female mice)				
	a. 1st litters	1	20,398	0.7 ± 1.4	
	b. 2nd litters	0	15,120	0.0	
6a	"284 R" effective dose chronic γ (0.009 R min^{-1} young female mice)	1	14,402	1.0 ± 1.9	
6b	"283 R" effective dose chronic γ (0.009 R min^{-1} old female mice)	2	13,742	2.3 ± 2.9	
7	400 R acute x ray (90 R min^{-1}) (age unreported)	23	13,842	22.1 ± 9.0	
8	400 R chronic γ (0.8 R min^{-1})				
	a. 2–4 mo. female mice 1st litter	7	16,760	6.0 ± 4.4	3–4
	b. 2nd litter	0	4,082	0.0	∞
	c. 6–9 mo. female mice 1st litter	11	40,944	3.8 ± 2.3	6
		12	9,094	18.9 ± 10.7	1
9	400 R acute x ray (age unreported) (8 × 50 R–75 h intervals)	19	27,906	9.7 ± 4.4	
10	400 R acute x ray (age unreported) (2 × 200 R 1 day interval)	9	6,086	21.1 ± 13.8	
11	600 R chronic γ (0.05 R min^{-1}) (7 week old female mice, 1 litter)	1	10,117	1.4 ± 2.8	
12	Control	3	204,639	0.2 ± 0.2	

[a] Reference: Items 1, 2, 3, 6, 7, 12 Russell (1977)
Item 4, 5 Lyon and Phillip (1975)
Items 7, 9 Russell (1968a)
Item 10 Russell (1965c)
Item 11 Carter (1958).

[b] 1 Group received: 4 fractions of 10 R d^{-1} at 2-h intervals for 5 days
1 fraction of 10 R d^{-1} each of 5 d wk^{-1} for 4 weeks, Russell (1977) computed effective dose of 172 R.

At still lower dose rates, the analysis is further complicated. First, the timing dynamics of oocyte maturation from immature to mature stages is not yet completely understood; second, the influence of radiation on this process and other physiologically related and integrated processes of the ovary needs to be worked out; and finally, by the fact that as the dose rate is lowered, the actual dose received by maturing cells is altered, since a substantial proportion of the dose may be received during the immature stage which, as described above, appears to have rather unique radiobiological properties. Thus, the nominal dose must be adjusted to reflect this complication. One method has been described (see Russell, 1977) by which the "effective dose" received by maturing oocytes under different radiation regimes is computed. By this method the "effective dose" after 400 R delivered at an exposure rate of 0.009 R min^{-1} is about 284 R (Item 6a and b, Table 4.7).

The frequency at 200 R for acute x rays (Item 4, young females) is about 2 times greater than for an "effective dose" of 207 R (nominal exposure 258 R) (Item 3) of chronic gamma delivered at 0.009 R min^{-1}. The 200 R data of older females (Items 2a and b) show an even greater effectiveness when compared to the 207 R chronic treatment.

The two experiments at 200 R of acute x rays, Items 2 and 4, have been performed in different laboratories, Oak Ridge and Harwell, respectively; but on ostensibly the same strain and are significantly different from each other, and the data were not pooled. Russell (personal communication) points out that Items 2 and 4 are not strictly comparable. Most of the data in Item 2 comes from females that were old at the time of irradiation, whereas the females used in Item 4 were not, a fact pointed out by Brewen and Payne (1979), who also recognized the significance of this fact in estimating mutation rates. Older females have shown consistently higher induced mutation rates (Russell, 1977). Russell states that for the females of corresponding age in both series the mutation rates are not significantly different.

We have, therefore, attempted, when possible, to separate the data both with respect to age and to provide the oocyte sensitivity from sequential litter data, two major factors of biological significance whose impact on mutation is as dramatic as the physical factors discussed. An inspection of the data comparing Items 2a vs. 2b, and 8c vs. 8d shows how remarkably different the rates may be in the same female for two different litters. Moreover, an interesting, and as yet unanswered, question is why the oocytes giving rise to second litters of young females appear to be less mutable than those which produce first litters while the reverse is true for oocytes in old females.

At 600 R (Item 11) delivered at 0.05 R min^{-1} (Carter, 1958; no

"effective dose" calculation was considered necessary by Russell, 1977) the per locus mutation frequency was 1.4×10^{-5}. No litters beyond the first were recoverable from young females in this experiment.

Russell (1977) has computed the slopes of the low-dose-rate data in several ways, the slopes are 0.17, 0.27, 0.33, and 0.44 times as effective as that for spermatogonia, only the last value for oocytes is significantly greater than the control. He also argued that the values of α and β computed for oocytes by Abrahamson and Wolff (1976) were wrong, that the α values particularly (for different control value) were too large and clearly did not predict the observed mutation rates for low-dose rate studies, and thus the approach employed by them was not valid for estimating hazards. Perhaps it is less a question of approach and more a question of using valid data appropriate to such an analysis, as will be demonstrated next. Russell was, of course, correct on this issue of slopes. Abrahamson and Wolff (1976) computed the α and β values from the acute dose data, unaware at the time (see above and Brewen and Payne, 1979) that the 200 R data was primarily from old females whose second litters (Item 2b) contributed the uniquely high mutation rate. For 400 R (the female ages were unreported) only mutation data from first litters were recovered (because of subsequent sterility) which would be similar to the results of young females. The 50 R data (Items 1a and b) (again female ages unreported) appear to show an increase, although not significant, between first and second litter, and thus may have an appreciable older female contribution. If the linear-quadratic equation is computed by using first litter 50 R and 400 R data, while substituting the 200 R data from young females (Lyon and Phillips, 1975), the equation for the per locus mutation rate is now:

$$I = 2.28 \times 10^{-6} + 2.81 \times 10^{-8}\, D + 1.15 \times 10^{-9}\, D^2 \qquad (4.6)$$

This equation provides an extremely good fit to the low-dose rate data, most of which appear to be from correspondingly young females; and seems to remove this area of disagreement.[8] Brewen and Payne (1979) clearly recognize the importance of separating different oocyte stage sensitivities and reanalyzed the data of Russell (1977) in a week-by-week analysis on the basis of quadratic kinetics using the model $I = C + BD^2$ since they assumed that the linear component would be small. For oocytes contributing to the first week per locus mutation rate they compute $C = 1.67 \times 10^{-6}$ and $B = 1.48 \times 10^{-9}$; for second to sixth week oocyte contributions, $C = 1.41 \times 10^{-6}$ and $B = 4.21 \times 10^{-9}$.

[8] Equation (4.6) becomes $I = 2.1 \times 10^{-6} + 6.0 \times 10^{-8}\, D + 0.9 \times 10^{-10}\, D^2$ when fitted to the newer data for 200, 400 and 600 R (Lyon *et al.*, 1979).

They conclude that the specific locus mutations are produced principally by a two-track process which they argue is further supported by the observations of Russell and Russell (1960) and L. B. Russell (1971) showing the association of deletions with the specific locus mutations in oocytes. Additional support for deletional nature of these mutations is derived from the more recent and elegant studies of L. B. Russell *et al.* (1979) on mutations associated with the albino region.

Brewen (personal communication) has advised that Lea's correction factor, G for the β value, should be introduced in computing the expected yields for the 8 fractions of 50 R exposure with 75 minute intervals and for the 400 R delivered at 0.8 R min^{-1}. The reason for employing G is that there can be interaction between the fractions in the former series and during the continuous 8 h exposure in the latter experiment. In addition, it is clearly required that the females in the 400 R fractionated series (8 × 50 R and 2 × 200 R) be correctly identified with respect to age and litter data to avoid misinterpretation of data. If the data are primarily from old females, then the coefficients α and β originally derived, 1.4×10^{-7}, 1.1×10^{-9} respectively, would still apply (Abrahamson and Wolff, 1976) Equation (4.6). Finally, it is of interest that the α/β value computed for specific locus events in oocytes of young females is 27 and the α/β values computed from Brewen's data on interchanges and deletions in oocytes are 16 and 44 respectively, the agreement, which some may consider fortuitous, should nevertheless be noted.

The reader's attention is next drawn to the fact that in every experiment reported there is a dramatic decrease in the number of progeny in second litters (Items 1, 2, 4, 5, and 8) relative to those produced for first litters by the same females. This is true regardless of age, dose, intensity, or fractionation sizes. Searle and Beechey (1974) have previously shown that the dominant lethal frequency (chromosome breakage leading to zygote mortality) is significantly increased in second litters of irradiated females, and this observation no doubt provides the explanation for this litter size reduction. Within this sample of maturing oocytes there appears to be some group which is extremely radiosensitive in the genetic sense, i.e., that produces high dominant lethal frequencies and contributes or could contribute to the higher mutation frequency (both specific locus and cytogenetic) under specific conditions. Russell *et al.* (1959) have already demonstrated that even very chronic exposures, 0.0084 R min^{-1} at reasonably low doses, 85 R, can cause very young females (about 2 weeks old) to be sterilized after their first litters. It is possible that these cells which may represent a smaller proportion of the maturing oocytes in older females contribute to this dominant lethality. If such a highly mutable

stage exists, is it also possible that experiments to date have failed to detect this stage? The answer could be yes for the following reason. Were this stage to persist for only 3 days at its level of high mutability such that an accumulated dose of, say, 20 R killed it, regardless of dose rate employed, it would have been eliminated without a trace of mutability. It is a fact that every oocyte experiment performed so far has delivered at least 10 R per day to any oocyte in the ovary, e.g., Lyon and Phillips (1975) irradiated at 10 R per day for 5 days each of 4 weeks, Russell's experiments at 0.009 R per day delivered about 12 R per day to oocytes. If this thesis has any credibility, it would suggest that it may still be premature to attempt to extrapolate mouse oocyte mutation data to humans. The techniques of both cytogenetics and genetics are, however, available to test this proposal. That there are cells in the mouse oocyte which have features in common with the presumptive high sensitivity cells just discussed, is the subject of the next unit of discussion, the immature oocyte.

All of the aforementioned oocyte data represented cells that were irradiated within six weeks of the time of ovulation (Table 4.7). The data for oocytes ovulated seven or more weeks after irradiation are presented in Table 4.8. Two features are immediately apparent from the data. First, there is an almost nonexistent yield of mutations. Second, for certain exposures, there is no survival of those oocyte stages which represent stages 1–3a (Oakberg's designation). An immediate question is, are these two phenomena related? Before attempting to provide the explanations proffered for these data, it may be of value to develop an overview of oocyte survival through all stages of development considered.

High exposures of acute irradiation, 400 R, or chronic 600 R (at 0.05 R min^{-1}) kill all oocyte stages beyond those giving rise to first litters. Thus, the second litter oocytes are more readily killed than more

TABLE 4.8—*Specific locus mutation frequencies in immature oocytes under varying conditions of exposure and exposure rate*

Item[a]	Exposure and manner of delivery	No. of mutants	Total F_1 Offspring	Per locus mutation rate ± 95% C.L. × 10^{-5}
1	50 R acute x ray (90 R min^{-1})	0	92,059	0
2	200 R acute x ray (90 R min^{-1})	0	351	0
3	258 R chronic γ (0.009 R min^{-1})	0	18,684	0
4	400 R chronic γ (0.8 R min^{-1})	0	176	0
5	400 R chronic γ (0.009 R min^{-1})	1	22,807	0.5 ± 1.2
6	423 R chronic γ (0.003 R min^{-1})	0	34,263	0

[a] References:
Items 1–5 Russell (1977)
Item 6 Batchelor *et al.* (1964).

mature cells. Lower exposures of acute irradiation, 300 R acute (Russell *et al.*, 1959) kill all the immature oocytes and drastically eliminate the stages of oocytes giving rise to second litters. The mean number of litters is 1.4; 200 R acute and 400 R chronic irradiation (at 0.8 R min^{-1}), regardless of female age, kill virtually all of the immature oocytes in stages 1–3a, first and second litters are recovered although there may be a reduction in the latter group. At still lower acute exposures, 50 R, 99 percent of the immature stages are killed but there are sufficient survivors to obtain more litters. This applies as well to 400 R delivered at 0.009 R min^{-1}, although the proportion of the population that are survivors is now known. Further, it can be noted (Table 4.9 taken from Searle, 1974) that the immature oocytes survive doses of 30 and 60 rads from neutrons and 80 rads from neutrons plus 58 rads gamma chronically delivered, but do not survive 120 rads of neutrons. With low-dose neutrons, fewer cells will be traversed by tracks and thus more survivors should be expected relative to equivalent doses of low-LET radiation.

Russell's (1967) considerations based initially on the neutron exposures were that selection, i.e., killing of cells traversed by single neutron tracks, eliminated the mutant cells, but based on the low-LET radiation observations, he suggested that "it seems unlikely that selection could be operating so rigorously as to eliminate every single mutation. To account for the extremely low mutation frequency in terms of repair seems more plausible for the following reason. The mutation frequency from low-dose-rate irradiation in the late oocytes is also extremely low, and here, killing is so infrequent that selection cannot be the explanation. In that case, repair seems to be involved, and it is so efficient at the lowest dose rate tested that the concept of a cell stage in which repair might be virtually complete does not seem far-fetched." On the basis of these same data, Searle (1974) and Abrahamson and Wolff (1976) concluded that it would be a remarkable repair system indeed that could virtually eliminate all of the mutational damage inflicted not only by neutron radiation, but also by low-LET exposure as well at a time when the vast majority of these cells were killed. They thus favored the alternate suggestion that selection was operating to eliminate mutations.

In summary, it would appear that there is valid evidence for assuming that the specific locus mutation rates in maturing and mature oocytes (stages 3b–8) will be influenced, i.e., reduced relative to unfractionated high intensity irradiation, by either low intensity exposures or multiply fractionated exposures with appropriate time intervals between the doses.

The shape of the acute dose-response curve in these oocyte stages

TABLE 4.9—*Frequencies of specific locus mutations after exposure of dictyate oocytes to fission neutrons*[a]

Irradiation-to-conception intervals	Absorbed dose (rads)	Absorbed dose rate (rad min^{-1})	Number of offspring	Value of mutations	Frequency per locus per 10^5 gametes	References
< 7 weeks	30[b]	8	5,870	1	2.43	Russell (1972)
	60	0.15	46,301	22	6.79	Russell (1965b; 1972)
	60	79	43,000	37	12.29	
	120	75	6,058	7	16.51	
						Russell (1972)
> 7 weeks	30	8	19,477	1	0.73	
	60	0.15	80,395	1	0.18	Russell (1965b; 1972)
	60	79	40,092	0	0.00	
	120	75	33	0	0.00	Russell (1972)
	138[c]	0.001	32,221	1[d]	0.44	Batchelor *et. al.* (1969)

[a] From Searle (1974), Table XIII.

[b] About one-eighth of each dose consists of γ-contamination (Russell, 1965b).

[c] About 80 rads of neutrons +58 rads of γ-rays, given over 12 weeks.

[d] In first litter.

is concave upward and different models have been presented to account for this observation. The shape of the dose-response curve for low-dose-rate exposures appears to be linear, but more extensive and well controlled data are needed. The conventional linear-quadratic formula $I = 2.3 \times 10^{-6} + 2.8 \times 10^{-8}D + 1.2 \times 10^{-9}D^2$, for specific locus mutations provides the coefficients that satisfy both types of dose-response curves under appropriate or comparable biological conditions (i.e., young females). The α coefficient for older females is 5 times larger. The evidence that dose rate and fractionation will correspondingly influence the mutation rate of the immature oocytes (stages 1–3a) is far less clear because of their extraordinary radiosensitivity.

The influence of the age of the female on both mutation rates of oocytes in different stages and perhaps also on the survivability of different oocyte stages becomes an increasingly important biological variable that must be well understood before the mouse oocyte studies can be extended to estimate human risk.

4.2.9 *Non-Mammalian Germ Cell Mutagenesis*

In mature and maturing male germ cells of *Drosophila*, dose-rate and fractionation effects are not to be expected for reasons discussed earlier. The dose-frequency response curve for sex-linked lethals has not been convincingly established for several reasons. The earlier studies, 1930–1960s, were carried out on heterogeneous samples of sperm and spermatids of varying sensitivities (see review by Sankaranarayanan and Sobels, 1976) and the studies from the same workers sometimes showed linear response; at other times the best fits required that a dose-squared component be introduced into the equation (Edington, 1956; Edington *et al.*, 1962). When a dose-squared contribution was found in virtually mature sperm, the inflection point in the curve was between 3000 R and 4000 R (Traut, 1963; Shiomi, 1967), i.e., α/β was generally 3500 R (Abrahamson, 1976) both for sex-linked lethals and chromosome aberrations. When a linear dose relationship was found in fully mature sperm (Gonzalez, 1972), the dose-response curve was carried out over a more limited exposure range (500–2500 R).

Inagaki and Nakao (1966) demonstrated that for specific locus visible mutations in *Drosophila* sperm, the frequency rose faster than linearly over an exposure range of 1000–4000 R, but they did not attempt to fit the data to a more complex equation. The per locus fit to the linear quadratic equation is $I = 1.0 \times 10^{-5} + 0.85 \times 10^{-8}D + 0.32 \times 10^{-11}D^2$, $(\alpha/\beta = 2600)$.

Studies on dose, dose rate, and fractionation in Drosophila sper-

matogonia and oogonia. Early studies by Oftedal (1964a,b,c) led him to conclude that at low doses the yield of mutations per unit dose (sex-linked recessive lethals) increased relative to higher doses examined. Oftedal invoked the model earlier developed by Muller *et al.* (1954), i.e., an unusually radiosensitive gonial population was recovered only at low doses. Attempts to verify this hypothesis by testing at even lower doses have failed to verify the Oftedal model, as will be discussed below. Abrahamson and Friedman (1964) carried out a dose-response sex-linked lethal experiment on spermatogonia at higher doses than Oftedal and concluded that the dose-response curve was linear. This conclusion resulted, however, from an artifact in the experimental approach. The authors assumed that fractionating the dose at very high doses in order to increase survival of spermatogonial cells would have no effect on the dose-response curve. Since the linearity concept was indeed an accepted view then, this procedure was never challenged.

The experiments of Abrahamson and Meyer (1976) and Meyer and Abrahamson (1978) and continuing studies on *Drosophila* oogonia, undertaken to test the Oftedal model and establish a dose-response curve over a wide range of exposures 20–6000 R, have shown that the data on sex-linked lethal mutations are fitted best by a linear-quadratic function (see Figure 4.14). The results do significantly differ from a

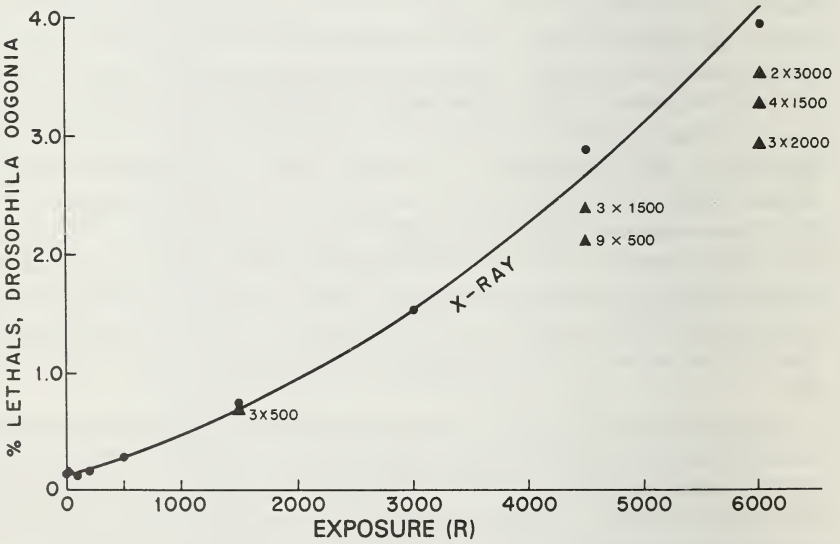

Fig. 4.14. *Drosophila* oogonial x-ray mutation rate data of Meyer and Abrahamson (1978). The solid circles represent single acute exposures and the solid triangles represent fractionated exposures as indicated on the figure.

linear model and provide no support for the hypothesis presented by Oftedal of a highly radiosensitive subpopulation of gonial cells. The experiments also provide an explanation for the studies by Muller *et al.* (1963) and Purdom (1963) on the effect of dose rate on mutation frequency in gonial cells.

The Abrahamson and Meyer (1976) experiment shows that the α/β value for *Drosophila* mutations in gonia are in the range of 3000 R. Thus, attempts to demonstrate dose-rate effects in these gonial stages at exposures in the range of 1000 R could hardly be expected to demonstrate such an effect, which was the conclusion reached by Purdom (1963).

Muller *et al.* (1963) were unconvinced that a dose-rate effect could be demonstrated in oogonia on the basis of their studies at 4000 R employing two exposure rates, 1 R min^{-1} or less, versus 7,333 R min^{-1}. As with Abrahamson and Friedman's (1964) studies, the experiments were confounded by employing fractionated doses with respect to mutation yield. When the data were reanalyzed (Abrahamson and Meyer, 1976) with this bias eliminated, the results indeed demonstrate a significant reduction in mutation rate by the low intensity radiation and the α coefficient derived from the linear-quadratic fit predicts quite closely the results obtained at the low-dose rate.

The unpublished fractionated exposure data (Meyer and Abrahamson, personal communication) also shown in Figure 4.14 demonstrates that all fractionated 6000 R exposures (2×3000 R; 4×1500 R; 3×2000 R) are significantly below the single 6000 R exposure with which they were run. (Since all of the fractionated experiments as well as the 3000 R and 1500 R single exposures were performed at different times, it may not be surprising to find that differences exist in these comparisons.) Fractionation studies at 1500 R and 4500 R are also consistent with the predictions of the linear quadratic model.

Silkworm studies. The early silkworm (*Bombyx mori*) studies have been reviewed in the book by Tazima (1964) *The Genetics of the Silkworm*, in which the author, who has pioneered radiation studies on this organism, describes the basic biology of mutation induction with this organism. The vast majority of the studies on germ cell mutability employ the detection of red and pink egg color mutants as an indicator of induced mutation at two specific loci. Since these mutations are recovered in eggs which may not be hatched for many months thereafter, it is frequently unclear as to whether the mutants are viable or will, in fact, be egg lethals, i.e., dominant lethals. In the early studies Tazima reports that, of the viable egg mutants, those that were able to be bred, about 80 percent were lethals in homozygous condition and he assumed that they were composed of a mix of gene

mutations (intragenic events) and deletions that extend to adjacent and nearby loci. In many of the more recent studies it is more likely that the yield of mutations also includes gross chromosome rearrangements that will lead to the category of dominant lethal mutations (Tazima, personal communication). Much of the more recent work by Tazima and his colleagues has been reviewed in the UNSCEAR (1966, 1972) documents. For the early primordial germ cells of males and females irradiated as young larvae, the now conventional dose-rate reduction has been observed. When, however, older larvae were irradiated, chronic exposures have been shown to be more mutagenic than acute exposures. Tazima (1969), based on extensive studies by him and his colleagues, has concluded that under the chronic dose rate conditions "the mitotic process of the cell is considerably inhibited, being blocked at G1 and G2 phases. This implies that the difference in mutation frequency between acute and chronic exposure is primarily a reflection of mutation rates at random and a selected sensitivity phase of the cell cycle."

Reminiscent of the mouse studies is the observation that in oogonia the dose response curve appears to be linear for both acute and chronic exposures over an exposure range of 500–2000 R, while for spermatogonia, both the acute and chronic exposures show a greater than linear dose-response (Tazima and Kondo, 1963). The oogonial cells are about 50 percent less sensitive than the spermatogonial cells and thus a higher dose range might be required to demonstrate a significant dose-squared component in oogonia.

In summary, the two non-mammalian systems that have received extensive studies, *Drosophila* and *Bombyx*, can be stated to show a dose-rate influence on mutation induction in germ cells. In *Drosophila,* conventional linear-quadratic kinetics can adequately explain the role of low-intensity and dose-fractionation modifications of mutation response. In the silkworm, other biological variables, under certain conditions, have been demonstrated to have an influence on the yield of mutations, in addition to dose rate *per se.*

5. Effects on Plants

Plant materials have been widely used for many years in experiments on radiation effects and have thus contributed importantly in the development of basic principles of radiobiology. From an analysis of x-ray induced chromosomal aberrations in microspores of *Tradescantia*, a favorable plant for cytogenetic investigation, Sax (1940) concluded:

> "Aberrations involving two chromosomes, or two loci in the same chromosome, are dependent upon two independent breaks, limited in both time and space. The frequency of these two-hit aberrations is dependent upon the radiation intensity. High intensity is more effective than low intensity because the aberrations are dependent upon two adjacent breaks within certain limits of time. The frequency of one-hit aberrations at a given dosage is independent of the time-intensity factor. The frequency of two-hit aberrations increases exponentially with increased dosage ... Intermittent dosage experiments show that broken ends of chromosomes may remain in an unstable condition for as long as one hour before fusion, although most fusions occur in a much shorter time. Only a small proportion of the x-ray induced breaks result in visible chromosome aberrations. Most of the broken ends reunite in the original positions with no evident alteration of the chromosome."

Giles (1943) showed, with the same plant material, that after neutron irradiation (7.5 to 15 MeV) the 2-break aberrations increased linearly with dose. This was attributed to both breaks being produced by single proton ionizing paths in contrast to their production with x rays by two independent electron ionization paths.

The account presented here will review the evidence from more recent experiments with plant material on the effects from low doses and low-dose rates of low-LET radiation. The plant data in general are included in this report, not only to make use of the wealth of highly quantitative dose-response data, but to show that the profusion of plant data all show conformity with basic principles of radiobiology as applied to man.

The results with five plant systems are described briefly below: (1) the production of yellow-green sectors in maize leaves; (2) growth inhibition in germinating seeds of barley; (3) bud production in *Saintpaulia*; (4) tumor formation in *Nicotiana*; and (5) pink "mutations" in *Tradescantia* stamen hair cells.

5.1 Maize yg_2 System

Seeds of a genetic stock of corn or maize (*Zea mays*) heterozygous at the yellow green locus (Yg_2/yg_2) were used in these experiments. Loss of the dominant Yg_2 allele (deletion) or change in its function (mutation) in heterozygotes gives a yellowish-green phenotype in leaf cells and cell lineages of the altered genotypes. The frequency of yellow-green sectors in leaves of seedlings grown from irradiated seeds was used as a measure of the frequency of radiation-induced change or damage. The seeds were irradiated with 250 kV x rays (1658–1845 rad min^{-1}) or fission neutrons. The range in doses for x rays was from 500 to 40,000 rads and for neutrons from 30 to 2690 rads.

The experimental results for one of the leaves, leaf 4, are shown in Figure 5.1 in a logarithmic plot of the frequency of yg_2 sectors per leaf as a function of absorbed dose (Smith *et al.*, 1974). The curves represent the least squares fit according to the equations:

$$y = (\alpha_x D_x + \beta D_x^2)\, e^{-bD_x^2} \quad \text{for x rays,} \tag{5.1}$$

$$y = \alpha_n D_n\, e^{-a_n D_n} \quad \text{for neutrons.} \tag{5.2}$$

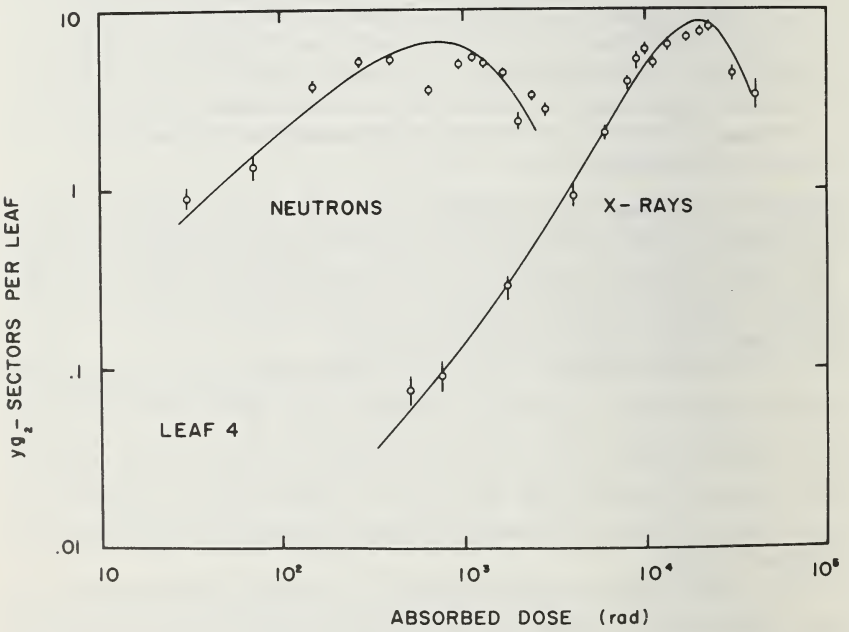

Fig. 5.1. Mean numbers of yg_2 sectors in maize leaf 4 as a function of x-ray and neutron dose (logarithmic plot). The vertical bars indicate standard deviations due to Poissonian fluctuations of the observed events. (From Smith *et al.*, 1974).

The yield, over the full dose range, is the product of the probability for mutation induction and the survival probability. Although there is an obvious paucity of data in the low-dose range, the slope of the rising part of the neutron curve may be consistent with unity and peaks at less than 1000 rads. The x-ray curve, on the other hand, may approximate a linear increase at the smallest doses and, with increased dose, shows evidence for a steeper slope, commencing in the vicinity of 2500 rads, as would be expected with an increasing quadratic component. The x-ray dose-response curve peaks at about 20 krads. The decline in the upper part of both curves is attributable to cell killing or loss of reproductive ability at high doses.

No dose-rate effect for x rays has been observed with this system over the range of 10.3 rad min^{-1} (278 min) to 1728 rad min^{-1} (1 min, 37 s) at a dose level of 2850 rads. It may be necessary to go to higher doses in order to show a dose-rate effect. However, since this is a dry seed system in which the metabolic rate is low, it may not be possible to demonstrate dose-rate or dose-fractionation phenomena. In addition, the target sites are exceptionally small under conditions of desiccation so that for doses that in most biological systems would be considered high, a response characteristic of low doses is obtained in the dry system.

5.2 Barley Seed System

Germinating seeds of barley were irradiated with ^{137}Cs gamma rays at various combinations of exposure (400–3200 R) and exposure rate (15.5–24,000 R h^{-1}) or duration of exposure (from about 1 min to over 100 h). Seedling height was measured 5 days after the initiation of irradiation and the various levels of growth inhibition produced by each combination of treatments were determined (Bottino *et al.*, 1975). Growth inhibition curves based on both exposure and exposure rate were constructed (Figure 5.2). As exposure rate increased, the effectiveness increased between 30 and 1500 R h^{-1} (0.03 to 0.3 h exposure time). Another way of expressing the meaning of these results is to select one level of damage, such as 30 percent growth inhibition, and note that to produce this effect at an exposure rate of 20 R h^{-1} required 1600 R total exposure, whereas at the much higher exposure rate of 1000 R h^{-1} only about 600 R are required. Above 1500 R h^{-1}, the effectiveness per R decreased in some cases. The reason for this response has not been determined, but it could, for example, be due to a reduced probability, with very short irradiation times, of hitting a sensitive target available for only a brief period during the cycle of

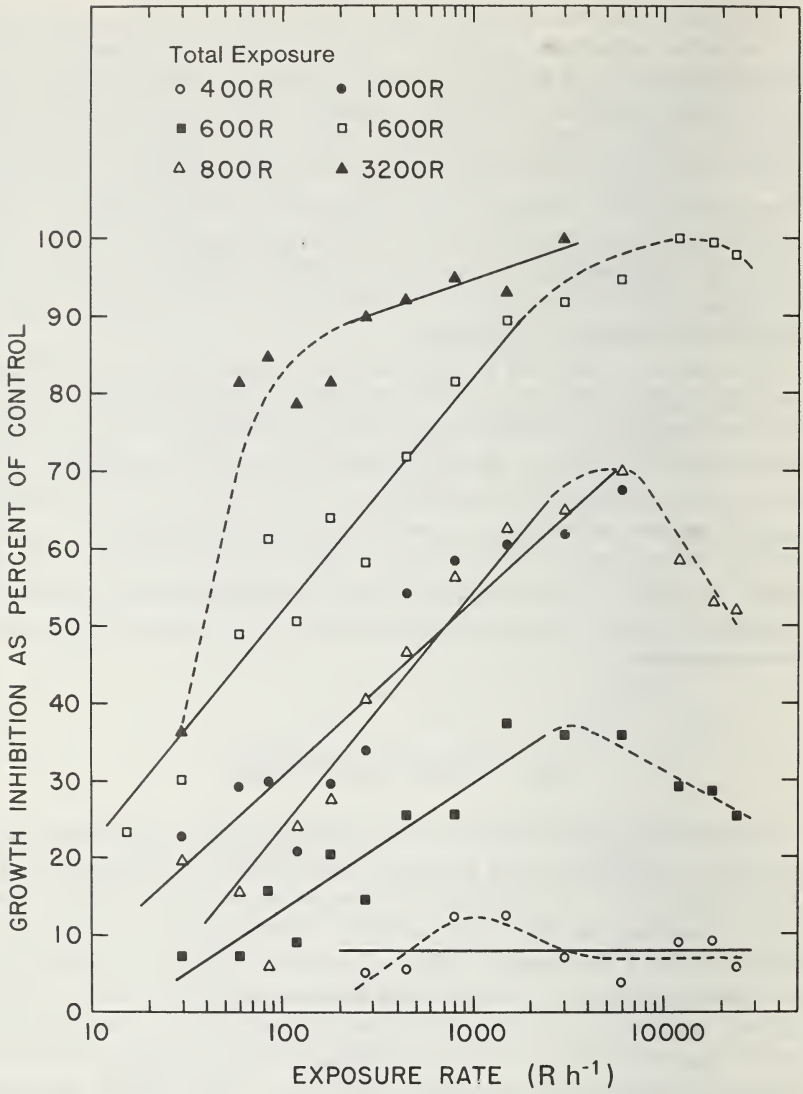

Fig. 5.2. Growth inhibition (percent of control) vs. log exposure rate (R h^{-1}) for germinating seeds of barley given six different exposures of ^{137}Cs gamma rays (From Bottino *et al.*, 1975).

cells in an asynchronous population. This point of change in effectiveness occurred well within one mitotic cycle.

Thus, the germinating barley seed system has provided abundant evidence of an interrelated influence on effect between magnitude of exposure to radiation and the exposure rate or the time interval within

which a given dose is delivered. The dose-rate effect is consistent with the generally accepted interpretation of repair of sublethal damage as a function of time and radiation intensity.

5.3 *Saintpaulia* System

Detached leaves of African Violet (*Saintpaulia*) were exposed to acute, chronic, and fractionated x irradiation (Broertjes, 1972). The effects were scored as production of plantlets per leaf. The results show a striking dose-rate effect (Figure 5.3). For example, 75 krad were required to reduce production by 50 percent when delivered at a rate of 2 rad min^{-1} but only 5 krad were required at a dose rate of 200 rad min^{-1}.

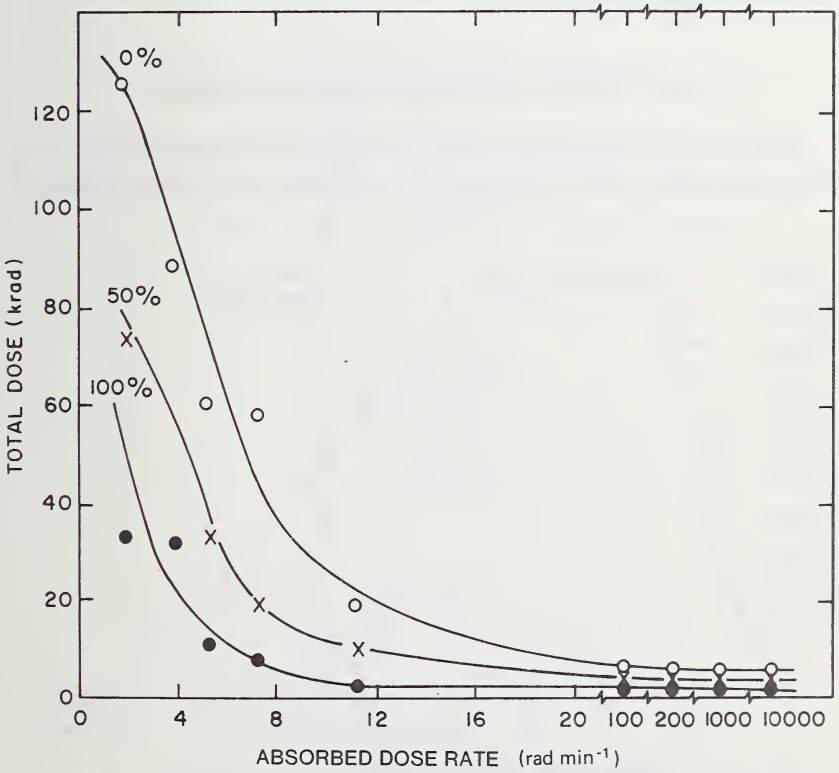

Fig. 5.3. Production of *Saintpaulia* plantlets per leaf, as a percentage of control, after various x-ray doses and dose rates (From Broertjes, 1972).

5.4 *Nicotiana* Tumor Induction

Certain hybrids between species of *Nicotiana*, the tobacco genus, are genetically tumor prone; i.e., all plants of a particular genotype will form tumors spontaneously when they reach a certain age. The time of initiating tumor formation can be greatly accelerated by exposure to ionizing radiation (Conklin and Smith, 1969). Young seedlings were scored for presence of tumors that formed within 21 days after exposure of the seeds to 250 kVp x rays (1500 rad min^{-1}) or to fast neutrons. The results are plotted in Figure 5.4. There is a clear dose dependency and 100 percent tumors are produced by a dose of 3 krad of neutrons or 30 krad of x rays. The RBE is roughly 10 throughout the dose range, including the region of declining effectiveness per rad at higher dose levels. These results are presented within the context of this report to show the similarity in response of plants to those of animals, with respect to the effects of radiation on tumor formation (see Figure 9.1).

5.5 *Tradescantia* Stamen Hair Mutations

The uses and advantages of the *Tradescantia* stamen hair system in demonstrating basic principles of radiobiology have been discussed

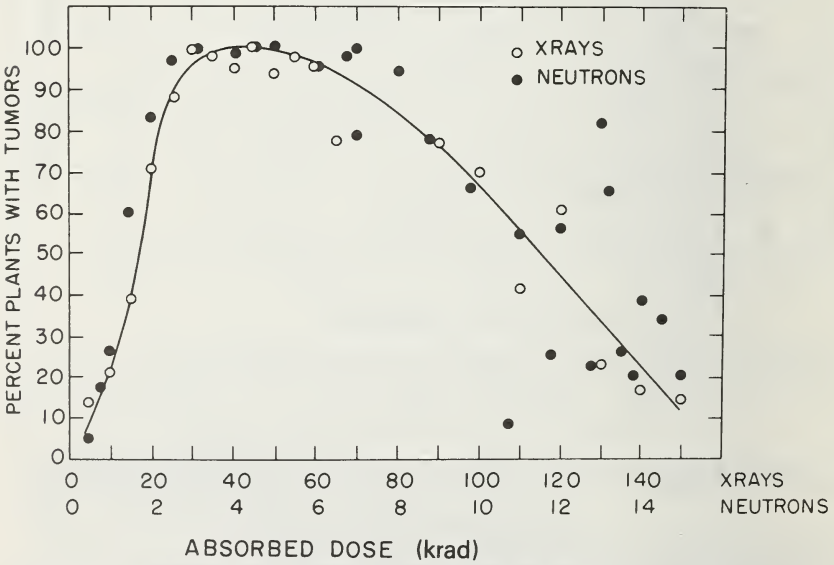

Fig. 5.4. Dose-response curves for tumor formation resulting from fast neutron or x irradiation of a genetically tumor prone *Nicotiana* hybrid (From Conklin and Smith, 1969).

TABLE 5.1.—*Computed values for α, β, and α/β for x-ray induced pink mutant events in two clones and three different experiments with Tradescantia*

Expt. no.	Clone no.	α	β	α/β	Reference
1	02	$5.7 \pm 0.53 \times 10^{-4}$	$17.3 \pm 3.45 \times 10^{-6}$	32.9 ± 7.22	Sparrow *et al.* (1972)
2	02	$4.6 \pm 0.31 \times 10^{-4}$	$5.5 \pm 0.92 \times 10^{-6}$	83.2 ± 15.1	Underbrink *et al.* (1976)
3	4430	$6.4 \pm 0.49 \times 10^{-4}$	$7.6 \pm 1.56 \times 10^{-6}$	83.1 ± 18.2	Sparrow *et al.* (1974)

in earlier Sections (2 and 3) of this report, and additional detail is provided here. Radiation effects have been studied mainly in a relatively radiosensitive clone that has the same range of sensitivity as mammalian cells for loss of reproductive integrity and may be more sensitive for somatic "mutation." The phenotypic effect that is scored as a mutation is the appearance of recessive pink colored cells in a heterozygous blue phenotype.

The tissues involved are hairs produced on stamen filaments, the structures that support the pollen-containing anthers. Within each flower there are 6 stamens, each bearing 50 to 90 hairs. Each hair is a chain of single cells and its pattern of growth is as follows: A cell in a stamen filament divides in such a way that one of the daughter cells protrudes obliquely out of the filament. This protruding cell is meristematic and becomes the terminal cell of the hair, continuing to divide until the mature hair (20 to 30 cells) is formed behind it. Thus, the

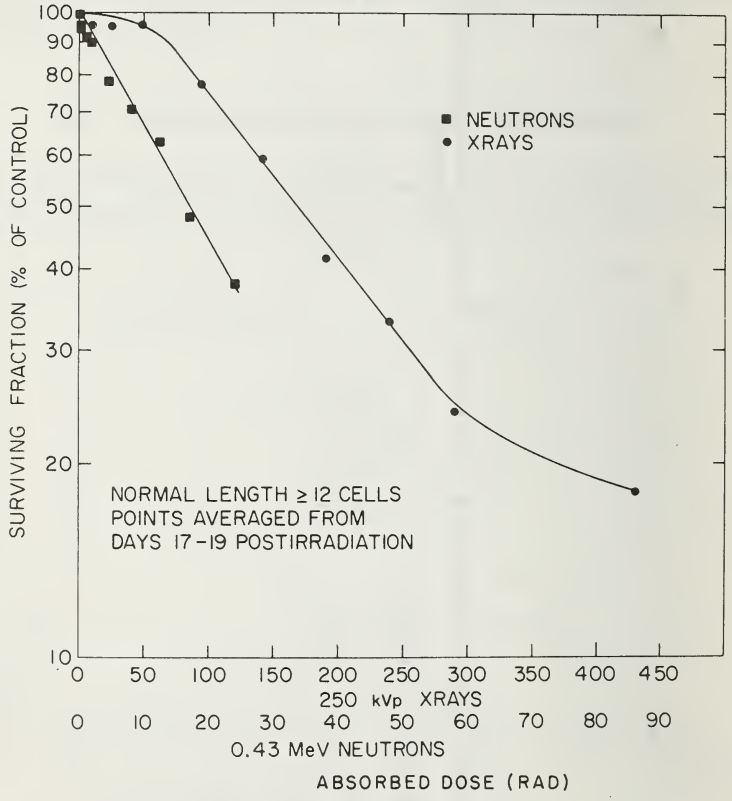

Fig. 5.5. Survival curves for stamen hairs after neutron and x irradiation. The surviving fraction is the percentage of normal length hairs as percent of control for the terminal third of the filament. The surviving fraction consists of hairs both with and without aberrations (From Underbrink and Sparrow, 1974).

hair is almost entirely the product of the single terminal cell. A single mutation from the dominant blue to pink color may occur early or late in hair development and produces, respectively, many or few mutant cells per hair. The pink "mutation" is most likely the result of loss of genetic material after radiation-induced chromosomal aberrations.

The control or background level in these experiments is about 6.5 $\times 10^{-4}$ events per hair. The "doubling dose," or amount of x irradiation to double the control level, is nearly one rad—a value considerably less than observed for certain effects in mammalian systems such as mice. As discussed previously in this report, the entire ascending portion of the x-ray curve can be fitted as the sum of a linear and a dose-squared term. The dose-response curve departs from linearity when the frequency of radiation-induced mutations is only about five times the spontaneous frequency. This emphasizes the conservative nature of linear extrapolations from larger doses in some systems. For example, the mutation frequency at one rad, estimated by the mutation frequency at 50 rads, would be more than twice as much as the observed rate.

The numerical values and the variability in estimates of α, β, and α/β in such favorable material as *Tradescantia* are illustrated in Table 5.1. The results from two experiments with the same clone (02) and

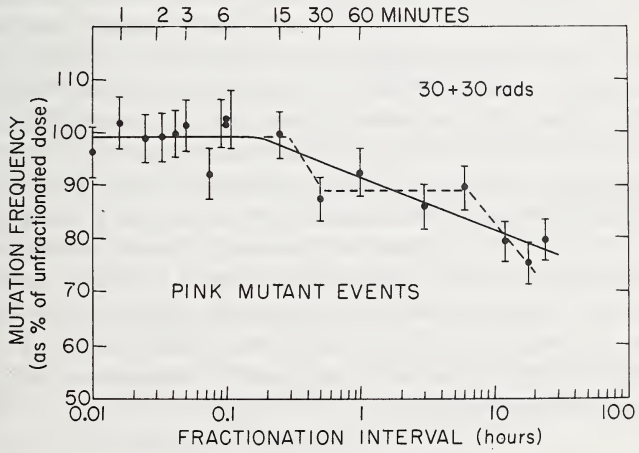

Fig. 5.6. Split dose response for pink mutant events in *Tradescantia* following irradiation with 250 kVp x rays. Data for the two 30-rad exposures as expressed as a percentage of the mutations scored following a single 60-rad acute exposure. The solid curve represents a best fit on the assumption that there is a linear relationship between mutations scored and the logarithm of time intervals between dose fractions of 15 min and longer. The dashed curve illustrates the possibility of a plateau extending from 0.5 to 5.0 hours (From McNulty *et al.*, 1977).

from two different clones (02 and 4430) are compared. Only data points from doses below 100 rads were used. Computations were made according to the equation:

$$\log I = \log [\alpha D + \beta D^2] \tag{5.3}$$

Mean values for α varied from (4.6 to 6.4) $\times 10^{-4}$, for β from (5.5 to 17.3) $\times 10^{-6}$, and for the ratio α/β from 32.9 to 83.2.

The descending portions of the curves shown for higher dose levels in Figure 3.1 are probably due to cell killing or loss of reproductive integrity. A plot of the surviving fraction of stamen hairs at a series of doses (Figure 5.5) shows a close correlation between the level at which the dose-response curves for mutation production begin to fall off more sharply and a marked reduction in survival (Underbrink and Sparrow, 1974). However, the question of the exact role of chromosome aberrations in determining loss of reproductive integrity remains unresolved and, in experiments set up specifically to investigate this point, no simple relationship between the two events was indicated (Davies, 1963).

The influence of dose fractionation on the induction of pink somatic mutations in stamen hair cells of *Tradescantia* was investigated with x rays (McNulty *et al.*, 1977). Inflorescences were exposed to a single acute dose of 60 rads and two acute doses of 30 rads each. The dose rate was constant at 30 rad min^{-1}. Intervals between dose fractions were varied from 35 s to 24 h, and the mutation frequency was compared with that resulting from a single dose of 60 rads. The data show a plateau of no effect of fractionation up to an interval of 15 min, and then a gradually decreasing effect up to 24 hours (Figure 5.6). It appears that, except at low doses, pink mutations include a component that results from the interaction of lesions produced by two independent radiation events. The damage from one event is less likely to be repaired before it can interact with damage caused by a second event in a single acute exposure than when there is a suitably long interval between the fractions. For the pink mutation phenomenon, this interval must be longer than 15 min and is increasingly effective the longer the interval. When the time is in excess of 24 hours, complications with the cell cycle time ensue.

6. Effects on Survival and Transformation of Cells *In Vitro*

6.1 Cell Survival

Techniques analogous to those for studying colony formation by single cells, as first applied to microbial systems, permit the assessment of the dependence of cell survival on various radiobiological parameters. In addition to usefulness in elucidating general radiobiological principles, cell survival studies also contribute to the analysis of etiological mechanisms. Changes in cell survival play a contributory role in mutagenesis, oncogenesis, and teratogenesis since, in each case, the endpoint requires one or more viable cells for expression. In the region of large doses, cell survival may play a dominant role, since the magnitude of the population capable of expressing altered properties may be appreciably affected by cell killing.

In contrast to the simple exponential dose dependence (exemplified by Curve IV of Figure 6.1) that characterizes the survival curves of certain bacteria and haploid yeasts, the shape of the low-LET radiation survival curve of mammalian cells is of the shoulder, or damage accumulation, type. In Figure 6.1, Curve I represents the shape of a dose-dependence frequently observed; *surviving fraction*, S, is observed to decrease with dose according to the modified multitarget scheme:

$$S = e^{-D/{}_1D_0}\left[1 - (1 - e^{-D/{}_nD_0})^n\right] \tag{6.1}$$

where ${}_1D_0$ is the inverse of the slope of the initial portion of the curve, ${}_nD_0$ is the inverse of the sensitivity of each of the n targets, and the inverse of the final slope D_0 is given by:

$$D_0 = \frac{({}_1D_0)({}_nD_0)}{{}_1D_0 + {}_nD_0}. \tag{6.2}$$

In the limit where ${}_1D_0$ is very large—that is, the initial slope approaches zero—Equation (6.2) shows that D_0 becomes equal to the multitarget value, ${}_nD_0$.

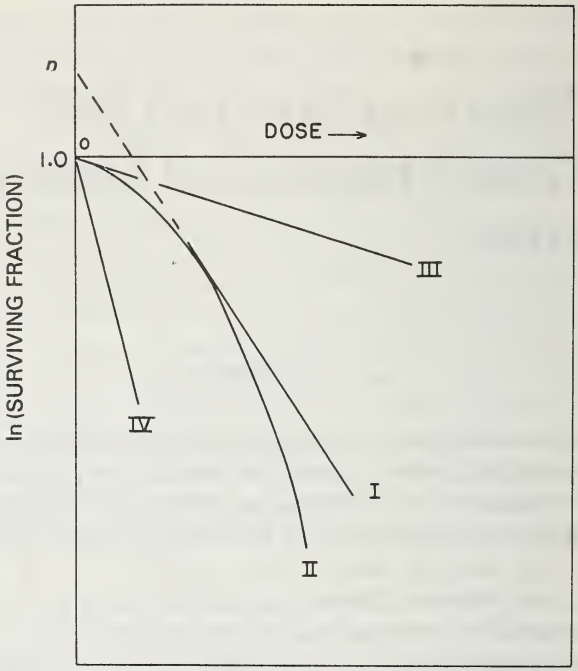

Fig. 6.1. Survival curve shapes according to Equations (6.1) and (6.3). Curve III represents the initial slope of Curves I and II and Curve IV is an example of exponential survival at a high LET.

Whereas Curve I in Figure 6.1 becomes exponential with increasing dose, Curve II portrays a continuously steepening slope and could be represented by:

$$S = e^{-(\alpha D + \beta D^2 + \gamma D^3 \cdots)} \tag{6.3}$$

Results have also been observed that can be fitted by this equation, frequently with only α and β greater than zero, and all other coefficients of D equal to zero.

In comparison with Figure 4.14, in which the incidence of successful events (e.g., the production of lethal mutations) is sketched, Figure 6.1 traces the dose dependence of "unsuccessful" events, in this case the dose-dependence of survival. The frequency of killed cells in the low-dose range of survival Curves I and II in Figure 6.1 can be plotted as curves similar to A or B in Figure 6.2, depending upon the presence or absence of a nonzero initial slope. Consequently, radiobiological parameters which may affect the shape of the initial part of a survival curve (Figure 6.1) may also be understood as having a corresponding effect on the killing curve (Figure 6.2). As already noted, dose-depen-

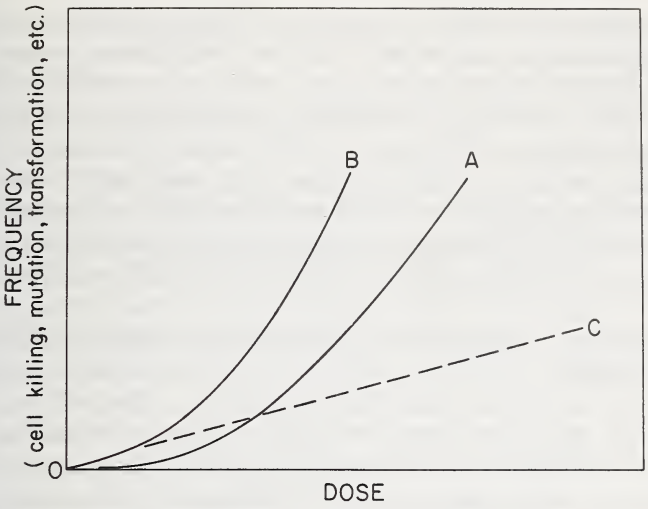

Fig. 6.2. Sketch of dose dependencies (x and γ radiation and chemicals) of the induction of altered cell properties in cultured Chinese hamster and human fibroblasts (rectilinear coordinates). Curve A has an initial slope of zero. The initial slope of Curve B is shown as Curve C.

dent changes in survival by themselves may have a bearing on the dose dependence of other endpoints. In addition, an understanding of the radiobiology of survival may help in the understanding of other radiation effects.

Regardless of which analytical expression fits a set of survival data, the downward curvature of a survival curve—or the upward curvature of a killing curve—means that damage must be accumulated to kill a cell. It follows that with increasing dose the probability becomes vanishingly small that a cell will survive without having suffered damage which could contribute to its demise. V79 Chinese hamster cells have been shown to be able to repair sublethal damage (Elkind and Sutton, 1959). Many subsequent observations (for example, see Elkind and Whitmore, 1967; Elkind, 1970) have made apparent two generalizations: 1) if the shape of a low-LET radiation survival curve indicates a requirement for damage accumulation (as do Curves I and II in Figure 6.1), surviving cells are able to repair sublethal damage; and 2) all mammalian cells capable of essentially unlimited division—i.e., cells grown *in vitro* and *in vivo*, and stem cells of cell renewal systems, as well as tumor cells—are able to repair sublethal damage.

Experimentally, repair of sublethal damage is made evident by the demonstration that two or more high-dose-rate, low-LET radiation exposures, the sum of whose doses exceed that for the initial portion

of the exponential survival curve for a single acute dose, are less effective than single exposures when separated in time, because in the interval between exposure there is a capacity for sublethal damage repair (Elkind and Sutton, 1959). This implies, as has been verified experimentally (e.g., Withers *et al.*, 1971), that irradiation at reduced dose rates results in higher survival over and above what might possibly reflect cell division during exposure. The result is that curves such as I and II in Figure 6.1 are shifted in the direction of Curve III; in respect to cell killing, Curve B in Figure 6.2 would be shifted toward C.

The shape of a mammalian cell survival curve changes qualitatively with increasing LET (Figure 6.3). The initial slope becomes steeper until at about a maximally effective LET (i.e., ~100 keV μm^{-1}) and beyond the curve becomes exponential as, for example, Curve IV, Figure 6.1. While it is not yet established that this change in shape represents a change only in ${}_1D_0$ in Equation (6.1), or α in Equation (6.3) with increasing LET, it is clear nevertheless that the capacity for sublethal damage (i.e., the shoulder width of the survival curve) and its repair are progressively reduced (Elkind, 1970; Withers *et al.*, 1970); and that, in general, the modifiers of radiobiological response become

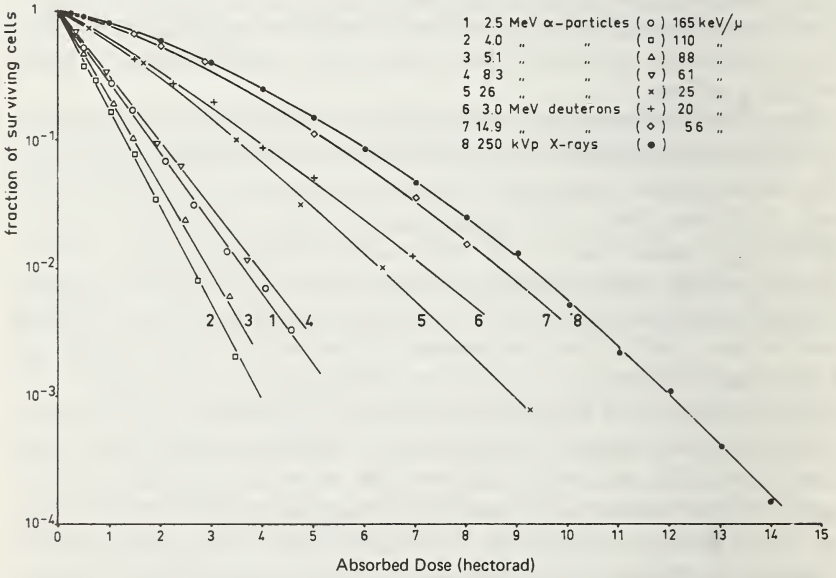

Fig. 6.3. Dose-survival curves of cultured T-1 cells in equilibrium with air, irradiated with mono-energetic heavy charged particles in conditions where narrow distributions of dose in LET are obtained (From Barendsen, 1968).

less effective (Elkind and Whitmore, 1967). Consistent with the transition to an exponential survival curve, the dose-rate dependence of high-LET radiation appears to be appreciably less than for low-LET radiations (e.g., Hall *et al.*, 1971; Withers *et al.*, 1971).

With respect to mammalian cell survival, the relative biological effectiveness (RBE) depends on both dose and dose rate. Because of the change in curve shape (Figures 6.1 and 6.3), RBE depends most strongly on level of effect in the small dose region. In addition, because with reduced dose rate low-LET curves (Figure 6.1) shift from I and II toward III, while curve IV may shift toward III only slightly, RBE at a given level of effect is a strong and inverse function of dose rate (e.g., Withers *et al.*, 1971).

The shift of curves such as I and II toward III (Figure 6.1), with decreasing dose rate, reflects repair of sublethal damage, as already noted. But a similar shift can be effected by the repair of potentially lethal damage (Hahn and Little, 1972). Operationally, a reduction in slope results when the conditions and/or the time course of the survival assay are appropriately changed (e.g., a delay in the assay) with no change in dose rate or dose schedule. Shifts to curves of lesser (or greater) steepness mean that cells are more able (or less able) to manage the potentially lethal damage after it has been registered. In the instance where the survival dependence is described by Equation (6.1), a decrease in the final slope (Figure 6.1) may mean not only that ${}_nD_0$ has increased, but possibly also that ${}_1D_0$ has increased. Where the survival curve is described by Equation (6.3), at least the coefficients of the higher powers of the dose would be expected to be less. It follows that a dose-rate dependence would probably be decreased under assay conditions which permit potential lethal damage repair.

This situation has the following important implications relative to the steepness of the initial slope of a survival curve (Figure 6.1) and, by analogy, to the initial slope of an induction curve (Figure 6.2). Changes in the steepness of a survival curve imply changes in damage expression. When a curve becomes less steep, it can be inferred that cells are more effective in their repair of damage. A decrease in D_0 may be due to a decrease in ${}_nD_0$, ${}_1D_0$, or both (Equation 6.2). Even if only ${}_nD_0$ changes in a given case, since $1/{}_nD_0$ is the sensitivity of a so-called "single-hit" process (in Equation (6.1) the "single-hit" inactivation of each of n targets), it follows that the sensitivity of the initial "single-hit" part of the curve $1/{}_1D_0$ in principle could also be modifiable by cellular processes. A similar statement applies to $1/\alpha$ in Equation (6.3). Examples of repair-mediated changes in exponential dose-response relationships can be found in the work with irradiated bacteria (e.g., Peak and Ainsworth, 1973; Yatagi and Matsuyama, 1977) and

animal viruses assayed in host cells having varying repair competences (e.g., Day, 1974).

For effects induced in the low-dose region, the situation analogous to that just described is a change in the steepness of the initial slope—e.g., of Curve B, Figure 6.2. Repair processes generally are found to be more effective at low- rather than at high-dose rates. Consequently, if in a given case the "single-hit" component of a radiation induced endpoint is dose-rate modifiable, one would expect Curves III or C, Figures 6.1 and 6.2, respectively, to become less steep.

Summary for Cell Survival: Cell survival, as judged by colony-forming ability, generally decreases as an exponential function of the dose with high-LET radiation and is weakly dependent on the dose rate. With low-LET radiation, on the other hand, the survival curve usually exhibits a shoulder in the low-dose region, the final slope being appreciably reduced at low-dose rates. The evidence implies that cells must accumulate sublethal damage during low-LET irradiation for impairment of survival. Accordingly, the amount of damage induced by a given increment of low-LET radiation will be appreciably less if delivered at a low-dose rate because of repair of such damage if suitable physiological conditions obtain.

6.2 Mutagenesis in Somatic Cells

The recent development of techniques for inducing mutant mammalian fibroblasts and lymphocytes in tissue culture has provided a potentially powerful tool with which to examine dose and dose-rate effects. In particular, studies of recessive X-linked mutations have proved useful, such as those involving the induction of 8-azaguanine or 6-thioguanine resistant mutants that are thought to be the result of a single, forward point mutation. Human, male-derived fibroblasts have been used in an x-ray study of the dose-dependence of the induction of 8-azaguanine resistance (Albertini and Demars, 1973). Similar types of studies have been done with V79 Chinese hamster cells and ultraviolet irradiation (Bridges and Huckle, 1970; Arlett and Harcourt, 1972); x and γ radiation (Bridges and Huckle, 1970; Arlett and Potter, 1971; Chu, 1971); as well as mutagenic and carcinogenic chemicals (Chu and Malling, 1968; Duncan and Brookes, 1973). In all of the foregoing, the dose dependence (rectilinear coordinates) is concave upward, as sketched in Figure 6.2.

However, the foregoing data have neither the resolution nor the precision to make clear whether, in some cases, a zero initial slope is obtained (Curve A) as opposed to a positive initial slope (Curve B).

More recently, Thacker and Cox (1975) and Cox *et al.* (1977) reported that human-derived normal fibroblasts are induced to 6-thioguanine resistance linearly with dose when either 250 kVp x rays or radiations of higher LET are used (e.g., α particles of 28 and 70 keV μm^{-1}, and fast neutrons produced by the absorption of 42 MeV deuterons in Be). Whereas dose fractionation has been shown to result in a reduced mutation frequency in V79 cells exposed to low-LET radiation (Arlett and Potter, 1971), similar studies have not yet been reported for human cells and no data are as yet available at reduced dose rates. Hence, even for a high-dose-rate dose-dependent curve (as depicted by Curve A in Figure 6.2), it is not known if the shape of the curve rises less steeply at low-dose rates for all types of cells. Similarly, there is evidence to indicate that under some laboratory conditions the slope of Curve C may not always be dose-rate independent.

6.3 Transformation

"Neoplastic" transformation in cultured cells is usually identified by a change in colony morphology. Cells derived from colonies containing evenly dispersed cells (i.e., so-called "contact inhibited cells") generally do not give rise to malignant tumors while transformed cells do. Thus, while the use of the *in vitro* transformation endpoint is recent and limited in the main to fibroblasts in culture, able to induce fibrosarcomas *in vivo*, it offers a quantitative measure for the study of cell specific changes responsible for at least one type of oncogenic change.

Radiation has been demonstrated to be capable of enhancing transformation due to other agents, even under conditions in which the radiation by itself is not observed to transform cell cultures. Thus, doses of x radiation well into the lethal range enhance the transformation of 3T3 mouse fibroblasts by SV40 virus, with a doubling dose of about 200 rads (Pollock and Todaro, 1968). Qualitatively similar results come from studies with cultured primary Syrian hamster embryo cells infected with SV40 virus (Coggin, 1969); and baby hamster kidney cells infected with polyoma virus (Stoker, 1965). In the study with 3T3 cells (Pollock and Todaro, 1968), selection by the radiation of cells more readily transformable did not seem to be involved, since the survival curve of the cells did not appear to depend upon viral infection or the time relative to infection when the radiation was given. In the case of cultured Syrian hamster embryo cells, radiation is also reported to enhance the frequency of transformation due to the carcinogen benzo(a)pyrene (Di Paolo *et al.*, 1971).

While the foregoing observations with viruses and a carcinogenic

chemical both indicate potentiation, they offer no insight into the shape of the radiation dose-dependence in the low-dose region or any possible dependence on dose rate. However, direct information is now available about the dose dependence of radiation transformation by itself and the possible influence of repair processes on transformation frequency. Primary cell cultures of Syrian hamster embryos are transformed after doses as small as 1 rad of x rays (Borek *et al.*, 1978; Borek, 1976) or 0.1 rad of fast neutrons (Figure 6.4). The x-ray dose dependence up to 75 rads suggests an upward curvature on a linear plot (i.e., similar to the curves in Figure 6.2), although the uncertainties are large enough not to preclude a linear dependence. For x-ray doses above 150 rads, the decreased frequency indicates that the particular cells susceptible to transformation are more readily killed than the bulk of the population, or that the transformation change renders cells more sensitive to killing, or that higher doses inhibit the expression of transformation. The first possibility is supported by dose fractionation results obtained with this system, since dose fractionation, which usually results in an increase in net survival, results in an increase in the frequency of transformants per survivor with little effect on overall

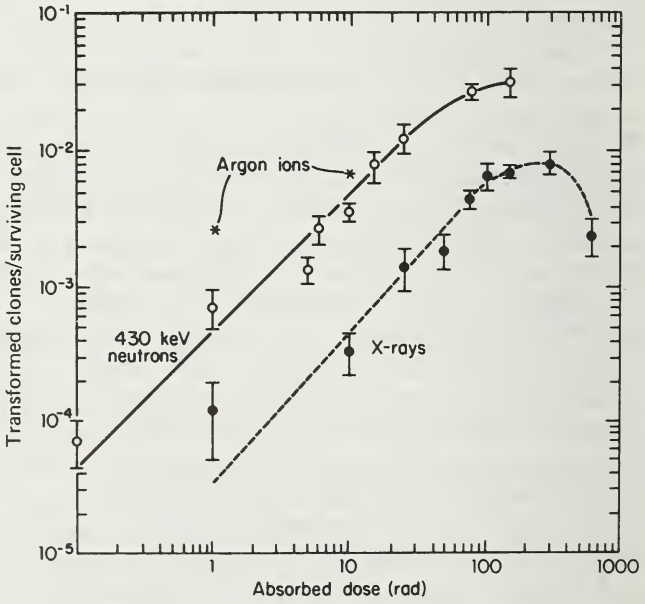

Fig. 6.4. Dose-response curve for cell transformation by x rays, neutrons, and argon ions. The data points plotted are the means of replicate experiments; and the error bars represent the standard error, or the error expected from the number of clones counted, whichever was larger. (From Borek *et al.*, 1978).

cell survival (Borek and Hall, 1974). However, these data do not assure that irradiation at low-dose rate would also result in enhanced transformation frequencies.

In C3H mouse embryo fibroblast cultures, so-called 10T1/2 cells, transformation has also been observed to result from x rays. The frequency of transformation per surviving cell increases with dose up to about 400 rads but does not decline at higher doses (Terzaghi and Little, 1976a; Han and Elkind, 1979) as was observed with Syrian hamster embryo cells. Fission-spectrum neutrons produce, with these cells, an induction curve having a similar shape (Han and Elkind, 1979). For 10T1/2 cells, it has been reported that fractional gamma irradiation with total doses less than 150 rads and a 5-hour interfraction interval results in about a two-fold increase in transformation per survivor (Miller and Hall, 1978). However, with larger total doses of photons a decrease in transformation frequency results (Terzaghi and Little, 1976b; Miller and Hall, 1978; Han and Elkind, 1979).

The results cited for Syrian hamster embryo cells and C3H 10T1/2 mouse cells do not, as yet, adequately address the questions of what effects low-dose fractionation and low-dose-rate continuous x radiation have on transformation frequencies. Where low total doses were used, increased frequencies were observed with both cell systems (Borek and Hall, 1974; Miller and Hall, 1978). When higher doses (Terzaghi and Little, 1976b) or intervals up to 16 hours were employed (Han and Elkind, 1979), reduced frequencies were observed. The latter results are in general accord with the x-ray induction of skin tumors in rats (Burns and Vanderlaan, 1977; see also Burns *et al.*, 1973; 1978). However, relatively large doses repeated after intervals long enough to permit some amount of repopulation as well as repair of sublethal damage can lead to enhanced tumor formation, as in the case of thymic lymphomas in mice (Kaplan and Brown, 1952).

Summary for Transformation: The "neoplastic" transformation of cells in culture increases in frequency with increasing radiation dose, reaching a maximum at moderately high doses. If the frequency is expressed per surviving cell, then the frequency may drop after still higher doses or remain constant depending on the cell system used. However, transformation expressed as a frequency per cell at risk—as would be the case for single-dose tumor induction—always declines after high doses in qualitative agreement with observations *in vivo*. The transformation of cells by carcinogenic chemicals or viruses similarly may be enhanced by radiation under appropriate circumstances. The influence of dose rate on the dose-response relationship for cell transformation remains to be explored. It appears to be established in several cell systems that fractionating the dose enhances the transfor-

mation frequency at low-dose levels, but leads to a sparing effect at doses above about 150 rads.

6.4 Somatic Mutation, Transformation, and DNA Synthesis Inhibition

The molecular biology underlying somatic mutation and neoplastic transformation is not completely understood. Nonetheless, correlations have been established between DNA damage, mutation, and transformation (or carcinogenesis) that are broad-ranging and consequently warrant examination.

To effect a change in the phenotype of a cell, it is a reasonable presumption that a lesion(s) must be registered in DNA and, as noted in Section 6.1, a changed phenotype presupposes that the effect of the inducing agent is sublethal or nonlethal. Painter (1977, 1979) has shown that the inhibition of (semiconservative) DNA synthesis in cultured HeLa cells may be used to identify bacterial mutagens. Inhibitors of DNA synthesis whose action is primarily metabolic (e.g., $NiCl_2$, dimethylsulfoxide, cycloheximide, or hydroxyurea) produce only a transient effect. In contrast, agents whose action results in breaks in strand continuity (e.g., ionizing radiation and alkylating agents), in intercalation between complementary base pairs (e.g., the antibiotics adriamycin and actinomycin D), or in base alterations and adduct formation (e.g., far-ultraviolet light and activated polycyclic aromatic hydrocarbons, respectively) produce lesions in DNA which result in the sustained inhibition of DNA synthesis. The last group has been shown to be linearly correlated, over 5–6 orders of magnitude (Painter and Howard, 1978), with their ability to produce revertants to independence of histidine for growth in histidine-requiring mutants of *Salmonella typhimurium* (Ames *et al.*, 1973, 1975).

The correlation between lesions in DNA, due to DNA interactive agents, and mutagenesis can be extended to a correlation between DNA interaction and carcinogenesis. An extensive survey of a wide variety of types of carcinogens and non-carcinogens has shown that 90 percent of the carcinogens are mutagenic in the *Salmonella* test and that few so-called non-carcinogens are mutagenically active (McCann *et al.*, 1975). The correlation between mutagenicity and carcinogenicity is linear and also broad, and extends over five orders of magnitude (Meselson and Russell, 1977). It has been shown that carcinogens which are mutagenic in *Salmonella* are also able to transform cultured mammalian cells (Purchase *et al.*, 1976).

Thus, from the preceding the following biological connections can be made with a high degree of confidence:

1) Ionizing radiation, non-ionizing radiation, and a variety of chemicals that interact with DNA in mammalian cells, and as a consequence produce a sustained inhibition of DNA synthesis, are bacterial mutagens. (Many of these agents also are mutagens in mammalian cells and in *Drosophila* germ cells, although the data available are not extensive enough to establish the extent of the correlation.)

2) Bacterial mutagens, in very high proportion, are carcinogens in experimental animals.

From these two points it may be inferred that the molecular and cellular biology of mutation and malignant transformation must be similar. Consequently, repair processes relative to mutation demonstrable, for example, by low-dose-rate exposure (see Figures 4.8 and 4.9) can be expected to be effective relative to transformation as well. With high-LET radiations, the dose-rate effect seems to be minimal for mutational events in all systems studied; and the same appears to be true for carcinogenic events as well.

6.5 Linear or Exponential Dose-Response Relationships

"Single-hit" inactivation derives from target theory which, in turn, rests on the discrete and random nature of the deposition of radiant energy. Historically, it was customary to assume that if a dose-effect dependence is linear, the particular endpoint under observation results from a single hit. Examples of linearity are: 1) exponential survival after large doses effectively is linear dose dependent in the region of small doses; 2) dose dependence of induced effects as illustrated by induction of chromosome aberrations with high-LET radiation; and 3) the initial dose portion of an induction process, the remainder of which may be fitted by higher powers of the dose. Mathematically, "single-hit" kinetics has been interpreted to mean that a target is affected if "hit" one or more times and if it is unaffected, it has not been hit (or damaged) at all. Radiation absorption being a quantized process, a linear dose dependence further has been taken to mean no dependence on dose rate; a linear dose dependence implies no requirement for damage accumulation. Hence, nothing will be repaired if the exposure time for a given dose is extended.

While the reasoning in the foregoing has become widely accepted, it is essentially circular. That is, if a linear dose dependence is observed, one concludes that this must have resulted from a single hit in a single

target. As a consequence, a role for biological processes capable of modulating the damage is excluded by the apparent absence of a requirement for subeffective damage. Hence, a dependence on dose rate is excluded because linearity is taken to mean an all or nothing process.

However, the observation that a particular radiation endpoint may be attributable to a single hit in a single target does not mean that all events in the target produce the effect. The mathematics justifying this statement are due to T. A. Hall (1953), whose derivation was cast in the framework of cell killing. The logic of his analysis is general, however, and has been further interpreted by Elkind (1977).

The probability of survival of a cell—assumed to have a single target and to be a member of a homogeneous population of cells—depends upon the product of two probabilities. The first is the probability that the target will suffer an energy deposition event. The second is the probability that such an event(s) will have an effect; i.e., inactivate the target and therefore the cell. The first probability may be derived from Poisson or binomial statistics. Hall derived the second to fit the requirement that an exponential survival relation results. (Consequently, a more general solution may exist, but if it does, it would include that derived by Hall.) This second probability may be called a "hit survival function," $H(h)$: it depends upon the number of events h in the target and a constant k, $0 \leq k \leq 1$; that is,

$$H(h) = k^h. \tag{6.4}$$

where $h \geq 0$ and can assume only integral values. It can be shown (Elkind, 1977) that when $k = 0$,

$$H(h) = \begin{cases} 1, & h = 0 \\ 0, & h \geq 1, \end{cases} \tag{6.5}$$

which constitutes the conventional biological statement of the necessary and sufficiency conditions for exponential survival. However, for $0 < k < 1$, $H(h)$ will be an exponentially decreasing function of h as shown in Figure 6.5.

The interpretation of Hall's theorem germane to this report is the following. A cell having a single target and being a member of a homogeneous population will survive exponentially if the probability of its survival as a function of the number of energy deposition events in its target is given by Equation (6.4). Homogeneity of the population is specified by: 1) the size (and composition) of the target in each cell being the same—thus, the probability of events in each target is the same; and 2) the constant k being the same for each cell. $(1 - k)$ is the probability that an event will score a "hit," that is, be effective. For

example, if the probability of each event being repaired is 0.5 (= k), a homogeneous population of cells will survive exponentially but with a slope one-half as steep as if each event had constituted a hit.

The foregoing may be readily cast in terms of other endpoints and applies equally to linear dose dependencies (i.e., a radiation-induced effect in which a small fraction of the population at risk is affected) and to exponential dose dependencies. In the instance of exponential cell survival, Figures 6.6 and 6.7 illustrate the influence on the slope of the curve resulting from $0 < k < 1$. The target volume v (Figure 6.6) is usually inferred from the slope of the curve. If the probability of

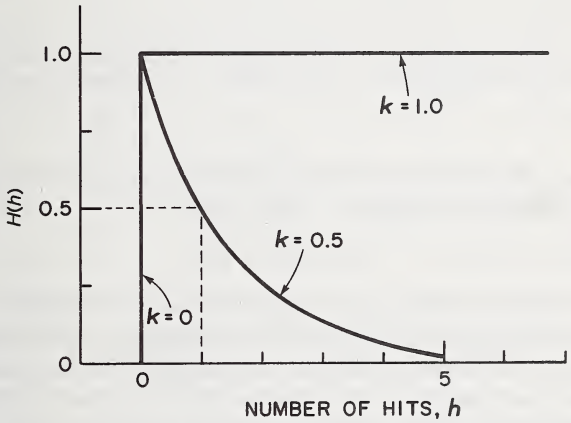

Fig. 6.5. The dependence of the hit survival function, $H(h)$, on the number of hits h for different values of k; $1 - k$ is the probability of effectiveness of a hit.

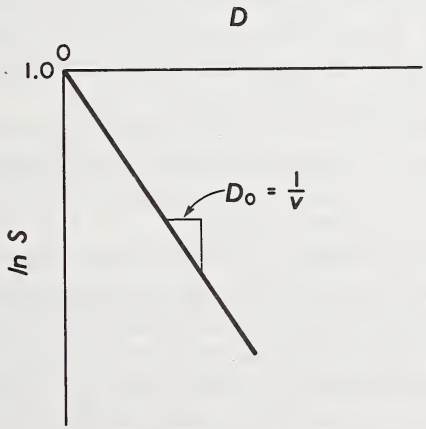

Fig. 6.6. The relationship between target volume v and the D_0 dose in the instance of single-hit inactivation. Dose is in units of hits per unit volume.

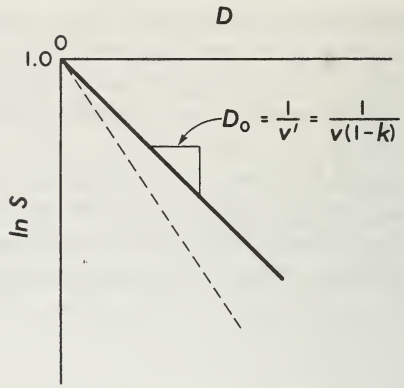

Fig. 6.7. The relationship between the observed D_0 and the apparent target volume v' $(0 < k < 1)$. The dashed curve would result if $k = 0$. Dose is in units of hits per volume.

effectiveness of an event lies between zero and one (Figure 6.7), the observed or effective volume v' is given by,

$$v' = v(1 - k). \tag{6.6}$$

Various interpretations may be made based on Equation (6.4) even within the constraints of population homogeneity (see Elkind, 1977). One, which is particularly relevant to this report, is the possibility that repair processes may have an influence even on linear (or exponential) dose dependencies. For example, if—as shown in Figure 6.5—the probability is 0.5 that an event in a target will be a hit because there is a 50 percent probability that any given event will be ineffective because it is repaired—i.e., both the probabilities of event registration as well as event repair are independent of the number of events registered—then $H(h)$ will decrease by 0.5 with each successive event. The result from Equation (6.6) is that $v' = v/2$.

Thus, to generalize, an event in a target may be only potentially effective. A linear (or exponential) dose dependence can result if the probability of each successive event being a "hit" is independent of the number of events in the target.

With respect to cell killing, examples of survival curves—the slopes of which represent varying degrees of potentially lethal damage expression are of two kinds. With bacteria, the results of Peak and Ainsworth (1973) and of Yatagai and Matsuyama (1977) illustrate that the slope of a survival curve depends upon the repair competences of an isogenetically related set of repair mutants of *E. coli* K-12 cells. This dependence is as evident for a low-LET radiation, such as ^{60}Co γ rays as it is for higher-LET radiations, such as fission spectrum neutrons,

α particles, and nitrogen ions. In the instance of ^{60}Co radiation, there is as much as a 9-fold difference in the slopes of the survival curves. Since it is highly unlikely that the target volume, v, is significantly different in *E. coli* K-12 mutants, all of which have essentially the same amount of DNA and other cell constituents, the conclusion follows that the expression of potentially lethal damage, and therefore the magnitude of k, varies among the repair-defective K-12 mutants. Further, it may be inferred that the magnitude of k reflects the repair competence of a particular mutant.

The second example of the modified expression of potentially lethal damage concerns cultured mammalian cells. Hahn and Little (1972) showed that the slope of an exponential survival curve depends upon the postirradiation treatment of the cells. In this example, no change in the genetic constitution is involved. Nevertheless, damage only potentially lethal under one set of postirradiation conditions is expressed if the conditions are changed, from which it may be inferred that the magnitude of k depends on the assay conditions.

Thus, Hall's theorem, Equation (6.4), supplies the theoretical framework for understanding a dependence of linear (or exponential) dose effects on dose rate. If repair competence, or postirradiation assay conditions, influence the apparent size of a target, it may be inferred that the magnitude of the dose effect depends upon dose rate. The reason for this is that biochemical and biological repair times ordinarily are long compared to exposure times of single high dose and dose rate exposures. When, at a reduced dose rate, the intervals between events become comparable to these repair times, a potentially effective event may be repaired before a second one is received. For a linear dose dependence, Hall's theorem requires that the probability of repair be independent of the number of events. The theorem does not specify, however, how—or if—the biological effect $H(h)$ depends on the inventory of events since time dependencies are not invoked. Consequently, if events are registered at a rate comparable to their repair, for a given dose the magnitude of $H(h)$ will be greater than for an acute exposure. In the context of cell survival, this means the survival at a low-dose rate would exceed that at a high-dose rate. For the low-dose-rate survival curve also to be exponential, it would be further required, in effect, that k increases but remains independent of dose.

The relevance of Hall's theorem to dose-rate dependencies may be summarized as follows. A linear (or exponential) dose dependence can reflect the expression of varying degrees of potentially effective damage. What proportion of the dose is ineffective may be governed by the capability of the biological system to repair or to bypass damage. When this is the case, exposure at reduced dose rates may give rise to

reduced effects. Dose-response relationships, which were linear (or exponential) at a given dose rate, may not remain so if the dose rate is changed (increased or decreased). Since rates of biochemical and/or biological processes which mitigate damage are usually slow compared to rates of damage registration due to high-dose-rate exposures, reduced dose rates would be expected to result in reduced biological effects.

7. Effects of Prenatal Irradiation on Growth and Development

The irradiation of the mammalian embryo or fetus can produce one or more of the following effects:

a) Prenatal death
b) Postnatal death during the:
   1. Neonatal and infant periods.
   2. Childhood, adolescent, and adult periods.
c) Development anomalies or malformations
d) Abnormalities of form and/or function involving:
   1. Growth retardation.
   2. Neurological damage.
   3. Reduced physiological performance.
   4. Sterility and reduced fertility.
   5. Increased risk of cancer.

The particular endpoint or type of response to be expected depends upon the gestational age when irradiated, the total dose, the dose rate, and the LET of the radiation. The level of response has been characterized for most lethal and teratologic effects in experimental animals for x-ray exposures given at relatively high-dose rates (> 10 rad min^{-1}) and total doses of 50 rads or more. Some responses have been well defined at doses as low as 5 rads. Overall dose-response relationships and the effects of variation in dose rate and LET have been extensively reviewed (UNSCEAR, 1977) and the reader is referred to that report for a nearly complete and quantitative summary.

If one extrapolates from studies with mice and rats, a brief or single high-dose-rate exposure of the human embryo to 5 rads or more of x or gamma radiation during early cleavage stages might be expected to increase the risk of mortality before or at implantation (~10–14 days post-conception); whereas if exposure is delayed until the second to the tenth week of gestation-during the period of major organ formation and cell differentiation-malformation and/or neonatal mortality are more likely effects (Rugh and Leach, 1974). Extensive human and animal experience also indicates that the period of organogenesis is a

susceptible period for the induction of growth retardation, microcephaly, and mental retardation (Brent and Gorson, 1972; Blot and Miller, 1973). Irradiation during the fetal period (10 weeks to birth) can induce a spectrum of deficiencies in postnatal growth, function, and viability, including the induction of leukemia and other cancers (UNSCEAR, 1972, 1977).

Information on both dose-rate and fractionation effects, while limited, indicates that the biological effectiveness of low-LET radiation is reduced at low-dose rates (Russell *et al.*, 1959; Brent, 1971), but this is confounded by the limited times ("critical" periods) during which organ systems are susceptible to teratogenic effects. In other words, stage sensitivity and total dose delivered during a sensitive period are also critical factors. The primitive germ cell (gonocyte) is the most radiosensitive cell type and the level of response depends upon the prenatal time period during which the gonocyte persists. The rate of gonocyte cell killing in mammals with long gestation periods (> 50 days), and therefore with long gonocyte lifespans, appears to depend only upon total dose and not upon dose rate even at rates down to one millirad per minute or less (Erickson, 1978).

The question of whether there is a threshold dose for radiation-induced malformations, retardation of growth and development, and/or prenatal lethality has never been satisfactorily answered.

Some reports (Rugh, 1971; Neumeister, 1978) have insisted that no threshold exists, and there are now data from a variety of measures that have identified biological injury in the fetus or newborn following exposure to either low single doses ($\sim$ 1 rad) at a sensitive stage or low-dose-rate exposures ($\sim$ 1 mrad min^{-1}) over most of the prenatal period. These measures include germ cell depletion (Dobson, 1976; Erickson and Martin, 1977), growth retardation (Michel and Fritz-Niggli, 1978), CNS damage or depressed CNS growth (Miller and Mulvihill, 1976; Martin and King, 1977; Cahill and Yuile, 1970), and cytogenetic abnormalities (Kirsch-Volders *et al.*, 1978).

Developmental abnormalities in mouse embryos repeatedly have been reported to result from x-ray doses as low as 5 rads administered in a single short exposure (Rugh and Crupp, 1959; Ohzu, 1965; Jacobsen, 1968); and the dose-response curves for induction of such abnormalities by acute x irradiation do not exclude a linear non-threshold type of response over the dose range up to 100 rads in mice of some strains (Jacobsen, 1968; Friedberg *et al.*, 1973).

It is obviously exceedingly difficult to identify and interpret the occurrence of small increments of injury since there is normally a wide variation in the spontaneous frequency of defects in both human and animal populations. It is, therefore, not surprising that human epidemiologic studies of the possible effects of variation in background

radiation on the incidence of malformations have thus far revealed no convincing evidence of association. In addition, careful examination of concurrent demographic and socio-economic factors has shown these to be of overriding importance in influencing the frequency of the abnormal conditions in question (Segall *et al.*, 1964).

A different type of finding has recently been reported from the Soviet Union. Studies with both chick and rat embryos have shown that exposure to low doses and/or low-dose rates at selected periods of development could act as a stimulant to growth and development (Kuzin *et al.*, 1975; Semagin, 1975). For example, chick viability, growth rate, and egg laying were all significantly increased at exposures of 1 to 3 R. Egg laying alone was 20 percent above the control at all exposures up to 10 R, then declined with further increase in dose. In the rat, cellularity of the cerebral cortex was increased at all low-dose rates (< 10 mrad min^{-1}). Results similar to these have been seen in a U.S. study of young women who had been exposed *in utero* to low doses of diagnostic irradiation (1–5 rads). The women exposed *in utero* had a significantly higher fertility rate than their matched controls (Meyer *et al.*, 1976). An originally observed excess of 15 percent is declining with age, however, so it is possible that lifetime reproductive history might eventually become equal to or less than the normal. These observations on enhanced viability and fertility are not easy to interpret and need to be confirmed.

The susceptibility of the human fetus to the leukemogenic and other tumorigenic effects of brief, low-dose exposure is discussed in Section 10. There are no relevant clinical data on dose-rate effects and apparently only one attempt has been made to correlate variation in infant and childhood leukemia mortality with variation in levels of background radiation (Mason and Miller, 1974). The results were essentially negative, although a 10 percent increase in the mortality ratio for childhood leukemia was noted for the high altitude (> 900 m), "partially urban," counties when compared to the total U.S. This deviation was not statistically significant.

Efforts to identify the etiologic mechanisms of birth defects have tentatively accounted for only about one-third of those observed; and the vast majority apparently can be attributed to random events during organogenesis. While background radiation could conceivably account for some portion of the total incidence, no quantitative evaluation is possible at present. In this connection, it is noteworthy that radiation levels significantly higher than natural background, such as medically related exposures, have been considered to account for less than 1 percent of the total number of congenital abnormalities seen in infants (Wilson, 1973).

Present concepts of environmental teratogenesis implicate basic

aspects of cellular injury, such as genetic or chromosomal mutation and cell death, in the induction of most of the lesions responsible for malformations, abnormalities of function, and other causes of pre- and post-natal mortality. Clearly, the experimental evidence from irradiation of the zygote, morula, blastula, and other early embryonic stages indicates that chromosome aberrations and mitotic inhibition are major factors in mortality because they lead to retarded growth, failures of implantation, and malformations (Wilson, 1973; NAS, 1972). Since the precursors of differentiating organs are clones that require some internal integrity, as well as the capability for morphogenic movement, the injury or death of isolated cells may not be as significant in the course of major organogenesis as in early cleavage stages, owing to the replaceability of such cells at the later stages. Based on our present knowledge of the cellular and tissue basis for prenatally induced injury, and our limited information about the influence of dose rate in this process, it is reasonable to assume that dose rate would generally influence the teratogenicity of radiation in much the same way as it influences the induction of mutagenic effects, chromosome aberrations, and cell killing.

Summary of Prenatal Effects: Injury to the embryo or fetus from prenatal irradiation can manifest itself in many ways, which may vary in kind, frequency, and severity depending on the stage of the embryo or fetus in its development at the time of irradiation, as well as on the dose, dose rate, and quality of radiation. Because of the diversity and complexity of such effects, many of which can be produced only by the injury or killing of a critical number of cells in sharply circumscribed stages of prenatal development, protraction of a given dose over a period of days or weeks may allow little of it to be received during the period when the organism is susceptible to the induction of a particular effect. To this extent, low-LET radiation can be expected to be reduced in effectiveness at low-dose rates. Because of the importance of stage sensitivity and the automatic limitations this places upon dose-rate/total dose considerations, there are no data of sufficient scope to allow a quantitative estimate of the reduced effectiveness of low-dose rates *per se*. However, because of the relative sensitivity of the conceptus, embryo, and fetus to low-dose levels, in terms of germ cell depletion and organ or whole body growth, attributing differences in degree of effect to "dose rate" could be misleading. Total dose during a given period of acute sensitivity does appear to be the principal determining factor for gonocyte killing.

8. Effects on Life Span

Radiation-induced life shortening is an easily measurable and precise biological endpoint. It is also an extremely complex endpoint, in that it measures the weighted deleterious effects of a variety of induced or accelerated disease processes. For this reason, it is useful as a "biological integrator" of deleterious effects.

Over the past two or three decades, extensive research has been conducted in a number of laboratories on the effects of radiation quality, dose, and dose rate on the survival time of experimental animals. More data are available for the mouse than for any other animal, but there is sufficient information from other species to establish certain generalizations that extend to all of the species studied. In the analysis that follows, data from mice have been necessarily drawn on most heavily. In addition, because there are major differences between dose-response relationships and dose-rate effects for low-LET and high-LET radiations, these types of radiation have been considered separately.

Ionizing radiation is somewhat unusual among environmental hazards in that much of the information on hazards to man derives from populations given a limited number of exposures at high-dose rates. This situation has led radiation biologists to think in terms of effects as a function of total dose. For most environmental agents, however, the important exposure parameter appears to be the daily or monthly exposure level throughout life rather than total dose (which will vary with individual longevity). Fortunately, there are data for mice irradiated until death at graded daily dose rates. As will be shown, there are some problems involved in relating the results of protracted exposures to those obtained with single, essentially instantaneous exposures, but these problems are not insurmountable in the dose ranges of principal interest.

As indicated at the outset, shortening of life is a complicated biological process, with radiation induced life span shortening in most mammalian studies at low and moderate doses being due essentially entirely to carcinogenesis, i.e., premature death due to the induction of tumors. Different species and different genotypes (strains) within species are known to vary with respect to their sensitivity to the induction of specific disease entities and different mouse strains show

variations in the degree of life shortening at equal radiation doses and dose rates. What is surprising is the relatively small magnitude of the variation between mouse strains or between species when appropriate scaling factors are used. Our primary interest here is not in the precise amount of life shortening at specific radiation doses, but rather the ratio of effectiveness for radiations of different LET or for radiations delivered at high- versus low-dose rates. The consistency of response under similar conditions makes it possible to use data from different laboratories to evaluate these ratios.

8.1 Dose-Rate and Dose-Response Relationships

Because of the time available for repair between ionizing events, one would expect the difference in effectiveness to be maximal when radiation delivered in a single exposure at a high-dose rate is compared with equivalent amounts of radiation delivered in a long protracted exposure at a very low-dose rate. The experimental data support the conclusion that these are, in fact, the limiting cases. A large number of studies have been conducted in mice exposed to graded doses of x or gamma rays delivered at high-dose rates. In general, the lowest dosage studied has been about 50 rads. In the range from 50 rads to acutely lethal doses, the dose-response curves are usually either linear or curvilinear upward. Because the sample sizes used have not always been adequate to distinguish between these relationships with great confidence, we can assume linearity for purposes of averaging the responses obtained in the various studies. Grahn and Sacher (1968) have summarized ten such studies involving about 20 strains of mice. Estimates of life shortening in days/100 rad ranged from 15 to 81, but the majority of values listed (9 of 14) were between 25 and 45 days. The unweighted average of all 14 estimates is 35 days. We can conclude, then, that for most mouse strains, life shortening following x or gamma radiation at a high-dose rate amounts to about 35 days/100 rad.

There is less information for mice exposed at very low-dose rates. The most thorough and systematic studies reported to date are those of Sacher and Grahn (1964), Grahn and Sacher (1968), and Grahn (1970). They exposed a number of mouse strains and hybrids to daily doses of gamma rays ranging from 0.3 to 56 rads. Exposures were initiated when the mice were 100 days old and were continued throughout life. The animals were actually irradiated for about 8 hours every day and the biological endpoint measured was the mean survival time (mean after survival or MAS) after the initiation of the exposures. The

fact that the irradiation was for 8 rather than 24 hours per day may introduce an important complication at higher daily doses. Thus, the MAS equaled the mean age at death minus 100 days. They found a remarkable consistency in the degree of shortening of the MAS between and among strains as a function of daily dose. The MAS declined exponentially with daily dose, d (in rad), and the equation

$$\text{MAS (treated)} = \text{MAS (controls)}\ e^{-0.04d} \tag{8.1}$$

adequately represented their data. At the lower daily doses they were unable to demonstrate consistently that there was significant life shortening. In some groups there appeared to be life lengthening. In other words, the possible effect was lost in the "noise" level of making such determinations. Since the exponential adequately fitted all of the experimental points, however, we can consider it the best estimate of the effect. To compare the results of this experiment with those where single brief exposures at high rates were used, it is necessary to obtain estimates of the total doses required at low rates to produce various levels of effect. Since radiation was given each day until death, the dose accumulated by each animal depended on its survival time. Thus, a wide range of total doses is represented in the populations exposed at any specified dose rate. The mean accumulated dose at each daily dosage level can be used, however, to compare the results obtained with those from studies utilizing single brief exposures. The mathematical relationships are as follows. Let

T_0 = mean after survival of the controls (days)
T_r = mean after survival (days) of mice irradiated at daily dose level d (rad)
D = mean accumulated dose (rad) at daily dose level d
S = loss of mean life span (days) at daily dose level d
$S = T_0 - T_r$

Equation (8.1) above becomes

$$T_r = T_0\ e^{-.04d} \tag{8.2}$$

At small values of d, the equation differs negligibly from:

$$T_r = T_0\ (1 - 0.04d) \tag{8.3}$$

Life shortening was defined as

$$S = T_0 - T_r \tag{8.4}$$

Substituting Equation (8.3) into Equation (8.4), we have

$$S = T_0\ (0.04d) \tag{8.5}$$

To obtain life shortening as a function of total dose ($D = T_r d$) we use the following approximation:

$$D \cong T_0 d \tag{8.6}$$

This approximation is reasonably good at doses where the amount of life shortening is small (where the exponential can be approximated by a linear relationship). Since

$$S = 0.04\ T_0 d \tag{8.7}$$

substituting Equation (8.6) into Equation (8.5)

$$S \cong 0.04\ D \tag{8.8}$$

In other words, in a restricted, relatively low dose range the extent of life shortening amounted to about 4 days/100 rad of accumulated dose.

A hypothetical illustration of the extent of life shortening predicted at small daily doses may be useful. Assume that a particular mouse strain lives an average of 750 days and that daily exposures are begun when the animals are 100 days old. The life shortening estimates from Equation (8.3) are shown in Table 8.1 for various small daily doses.

From Equation (8.1) relating mean after survival to daily dose rate, it follows that the degree of life shortening will vary somewhat with the natural (control) longevity of the particular mouse strain. For example, a hybrid showing a control mean age at death of 850 days would be predicted to show 15 days life shortening at 0.5 rad d^{-1} while a short-lived inbred strain surviving 500 days would show 8 days life shortening. This variation has a negligible effect on the equation relating life shortening to total dose, however, since the greater longevity results in a greater total dose.

The relative effectiveness of radiation delivered in a brief single exposure to protracted exposures (small daily doses over most of the lifetime) is given by the ratio of the slope constants (0.35 d rad^{-1} = coefficient for high dose rate; 0.04 d rad^{-1} = coefficient for low dose rate or 0.35/0.04 = 9). Thus, we conclude that, in mice, the single brief

TABLE 8.1—*Life shortening estimate from Equation (8.3) for various small daily doses. Irradiation was begun at 100 days of age*

Dose rate (rad d^{-1})	Mean age at death (d)	MAS (d)	Life shortening (d)	Mean accumulated dose (rad)
0	750	650	—	—
.1	747	647	3	65
.2	745	645	5	129
.3	742	642	8	193
.5	737	637	13	319
.8	729	629	21	503

exposures to low-LET radiation were about 9 times as effective as the same total dose given in a long protracted exposure. Allowing for uncertainties, we conclude that protracted exposures are ⅕ to ⅒ as effective in the mouse as single, high-dose-rate exposures (at total doses greater than about 50 rads) if linearity of life shortening with dose is assumed for both cases.

It is known that the sensitivity to radiation-induced life shortening decreases with increasing age in mice; and it is not yet clear to what extent the lessened effect of long-protracted exposures may be due to this age-dependent decrease in sensitivity. For this reason we are simply estimating the extent of the protraction effect without making any assumptions about the role of single event versus multiple event injury, repair, or changing sensitivity.

In the foregoing we have assumed that we were examining the limiting cases (highest and lowest life shortening) of the dose-rate effect. It is important to determine whether there are known exceptions to these extremes or whether other exposure patterns give results that are intermediate between these two cases. Under certain circumstances, fractionated exposures (large doses/fraction and total doses) can produce carcinogenic effects greater than those produced by the same dose given as a single exposure. For example, the appropriate fractionation schedule using large fractions may increase the incidence of thymic lymphomas in mice (Kaplan and Brown, 1952). There does not appear to be any case, however, where fractionation of low-LET radiation has resulted in significantly greater life shortening than is seen with single exposures. In general, closely spaced, large fractions are about as effective as a single dose. As the interval between fractions is prolonged and/or the dose per fraction is reduced, the life-shortening effect falls between the extremes discussed above. Similarly, protracted terminated exposures in the range of more than about 5 rad d^{-1} produce life shortening that lies between these limits. It seems likely, then, that the limiting upper case (maximum effect) is seen when single exposures at high-dose rates are given. We need to consider, however, whether protracted exposure until death at low-dose rates represents the lower limit (minimum effect).

There is the possibility that terminated exposures at low-dose rates are less effective in life shortening than an equal total dose spread over the life span. Such an effect might be anticipated if removal from the radiation field allowed repair processes to reverse incipient (e.g., premalignant) deleterious changes. On the other hand, exposures throughout life might be less effective if the radiation injury received late in life did not have time to express itself (e.g., as a neoplasm) before death from other causes occurred. The difficulty is that when termi-

nated exposures are made at low-dose rates (up to a few rad d^{-1}), significant effects on survival time cannot be detected (just as in the case of exposure until death at very low rates). At the present time, then, we are unable to conclude that there are exceptions to our assumption that we were dealing with limiting cases.

In the preceding section we assumed that the dose-response curve was linear with no threshold for doses above 50 rads delivered at high-dose rates. Until recently no experiments had been reported for the low-dose range in which sample sizes were adequate to choose among various alternative dose-response relationships. Storer *et al.* (1978) have reported on the effects on the longevity of RF female mice exposed to gamma rays or fission neutrons delivered at high or low rates. A total of about 27,000 mice were used. Of these, 16,000 were included in an experiment where graded doses of gamma rays delivered at 45 rad min^{-1} were employed. Dose levels, mean ages at death, and life shortening are shown in Table 8.2. To fit regression relationships to mean ages at death as a function of dose, the mean ages were weighted by the inverse of their estimated variances and lines were fitted by the method of least squares. Linearity could convincingly be rejected ($P < .001$) for the dose ranges 0 to 400 rads and 0 to 50 rads. No simple function adequately described longevity as a function of dose over the entire dose range, but in the range of principal interest (0 to 50 rads), longevity decreased as a function of dose squared ($P < 0.7$). The intercept constant of 634.9 (days of age) did not differ significantly from the observed control survival time of 634.7 days. The full equation is:

$$I = 634.9 - .0335\, D^2 \tag{8.8}$$

TABLE 8.2—*Mean ages at death and life shortening in mice exposed to gamma rays at 40–45 rad* min^{-1}[a]

Dose (rad)	Mean age at Death (days ± S. E.)	Life Shortening (days ± S. E.)
0 (controls)	634.7 ± 2.9	2.0 ± 4.2
10	632.7 ± 3.1	23.9 ± 6.0
25	610.8 ± 5.3	82.9 ± 6.0
50	551.8 ± 5.2	100.3 ± 11.7
75	534.4 ± 11.4	98.0 ± 6.1
100	536.7 ± 5.4	148.3 ± 6.5
150	486.4 ± 5.8	162.0 ± 20.1
200	472.7 ± 9.7	218.1 ± 3.9
300	416.6 ± 2.7	241.0 ± 7.9
400	393.7 ± 7.3	

[a] From Storer *et al.* (1978).

where I equals the mean age at death and D equals the total dose in rad. By forcing the regression through the zero dose intercept and changing the sign of the slope constant, life shortening could be described by: Life shortening (in days) = $0.0335\ D^2$ in the region of 0 to 50 rads.

It should be noted that the amount of life shortening reported is very much greater than that seen in other studies. The authors attribute this greater effect to the fact that the mice were maintained in a "barrier" facility with a rigidly controlled microbial environment. Why this environment should increase the sensitivity to life shortening is not known. In any case, it is unlikely that data from an experiment with comparable sample sizes will be forthcoming in the foreseeable future. For this reason we conclude that the best available evidence on the shape of the dose-response curve in the range below 50 rads indicates a dose-squared relationship (or more likely, a second order polynomial of the form: life shortening = $aD + bD^2$).

It is known that in many strains of mice, males show considerably less life shortening than do females exposed to the same radiation dose. The reasons for this sex difference are not known, but it has been suggested that the exquisite radiation sensitivity of the mouse ovary results in an endocrine imbalance that contributes to life shortening (Grahn, 1960). The female mice used by Storer *et al.* (1978) might not be representative of the general case for radiation responsiveness. To explore this point, Storer *et al.* (1978) also collected data on the survival times of male mice of the same strain exposed to a similar range of radiation doses. The sample sizes were considerably smaller (total sample of about 2000 mice) and for this reason it was not possible to choose rigorously among various possible dose-response relationships. It was possible, however, to show qualitative agreement with the data obtained for females. The results were as follows. At doses of 10 and 25 rads, there was some (but not statistically significant) life lengthening. At higher doses, there was life shortening, but not nearly as much as seen in the female mice. Linearity of the response could not be rejected nor could several other relationships. In the dose range of principal interest (0 to 50 rads) a linear relationship could not be rejected, but a dose-squared regression gave an improved fit. The improvement in fit with a polynomial approached statistical significance at the 10 percent level of probability. On the basis of these results, we conclude that there is no major qualitative difference in the results for the two sexes in the dose range of interest.

When radiation is delivered at low-dose rates, the dose-response relationship is more nearly linear. In the studies of Sacher and Grahn

(1964) discussed earlier, the life shortening increased as an exponential function of dose rate, but at the lower rates a linear relationship adequately approximated the dose-effect curve (Figure 8.1). In the largest study to date for a single mouse strain, Storer *et al.* (1978) found that terminated exposures made at the intermediate range of 8.3 rad d^{-1} (0.006 rad min^{-1}) yielded a linear response over the range of 50 to 400 rads with the line passing through the zero intercept. This finding is consistent with reports of other authors (e.g., Upton *et al.*, 1967) using terminated exposures of low- to intermediate-dose rates. As dose rates increase, however, the slope constant also decreases until it is impossible to distinguish it from zero slope at very low rates. The data are consistent with a linear relationship between life shortening in mice and total dose when radiation is delivered at low rates.

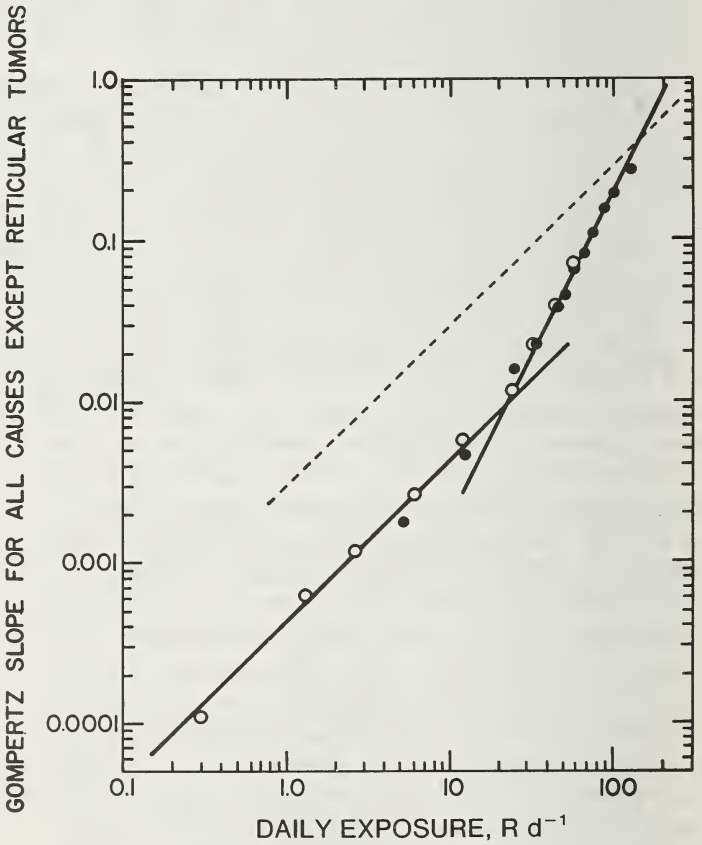

Fig. 8.1. Increase of slope of Gompertz function over control for LAF_1 mice (solid circles; Sacher and Grahn, 1964) and $B6CF_1$ mice (open circles; Grahn, 1960) given duration of life exposure to ^{60}Co gamma rays. The fitted line for daily fast neutron exposure is also shown (dashed line) (From Sacher, 1976).

The combination of dose-squared (or polynomial) function at high rates and a linear function at low rates complicates estimates of the magnitude of the dose-rate effect since the effectiveness will vary with total dose. As the total dose decreases, the estimates of life shortening will converge (if the high-dose relationship is second order, the effect of that term becomes negligible at very low doses). The point at which the dose-rate effect essentially disappears lies in the very low dose region where logistics make it difficult if not impossible to detect significant effects. For these reasons we conclude that the only possible method of estimating life-shortening effects for low doses (below about 5 rads) delivered at high-dose rates is to extrapolate by using the low-dose-rate relationship. For example, if 100 rads of radiation at a high rate produces 35 days of life shortening and 100 rads at a low rate is ⅛ as effective, then life shortening at the low rate would amount to about 0.04 days per rad. We would then estimate that 5 rads delivered at a high rate would yield $5 \times .04 = 0.2$ days life shortening based on a linear extrapolation from the low rate effectiveness. In summary, we conclude that radiation doses of less than about 5 rads delivered at a high rate are ⅛ to 1/10 as effective per unit absorbed dose as high total doses delivered at high rates.

8.2 Apparent Life Lengthening at Low-Dose Rates

An issue that has created some interpretive uncertainty (e.g., see Henry, 1961) in the study of radiation-induced life shortening concerns those observations where life lengthening has occurred following exposure to low levels of single or protracted doses of radiation. The first significant occurrence of this phenomenon can be found in the studies of Lorenz *et al.* (1954, 1955) who observed that mice exposed to 0.11 R d^{-1} for their life had a mean life expectancy slightly greater than their controls, which were housed separately. Similar findings have been reported by others, although not consistently, for animals under long duration low-level exposure (Carlson *et al.*, 1957; Sacher and Grahn, 1964; Grahn, 1970). The question then is how to reconcile these experimental results with the generally more frequent observation that life shortening has been induced at low doses.

Examination of the data reveals several significant characteristics. One, statistical analysis of the distribution of deaths and the associated life table parameters has demonstrated that the control animals have usually shown a greater variance around their mean life expectancy than was seen in the comparison low dose groups; and a more shallow or irregular regression of mortality rate on age was noted in controls.

These features are also accompanied by a reduction in the rate of intercurrent mortality from non-specific and infectious diseases among the irradiated animals during their early adult life, which was then usually followed in late life by a dying out at a rate greater than the controls (see Sacher [1956] for an analysis of the Lorenz data, for example). Second, the experiments cited were generally executed or initiated about 20 years ago when standards of laboratory animal care were considerably less rigorous than they are today and when infectious diseases were often a predominant factor in overall mortality.

The biological mechanism(s) involved have been discussed by Sacher and Trucco (1962) and have been recently reviewed by Sacher (1976). In essence, improved survival under low level irradiation can be interpreted as a favorable response to low grade injury, leading to some degree of systemic stimulation. The phenomenon has long been recognized in pharmacology for various agents. Actual life lengthening or prolongation beyond the normal expectation is not induced according to this interpretation. Instead, the exposed animals are prompted to achieve more nearly their normal life expectancy while their controls languish under suboptimal conditions. In these situations, genetic constitution may also be important, since inbred strains with a high susceptibility to infectious disease have been more likely to show this phenomenon than more vigorous hybrids or outbred lines. Whatever the correct interpretation may be, there appears to be little doubt that mean life span in some animal populations exposed to low level radiation throughout their lifetimes is longer than that of the unirradiated control population.

One other characteristic of this "over-survival" response has been its poor experimental predictability, since the reaction has always involved some degree of interaction among such concomitant physical and biological variables as (1) strain or genotype; (2) level of exposure; (3) types of caging; (4) ambient temperature; (5) crowding; (6) infection pressure; and (7) stress conditioning.

8.3 Interspecies Comparisons

There are some data on the effects of radiation on longevity for a number of mammals including man. In general, the data from experimental animals, principally rats, guinea pigs, and dogs (Tables 8.3 and 8.4) are qualitatively in agreement with some of the conclusions reached above for mice. For example, it is clear that in these other species low-LET radiation delivered at low rates is less effective than

TABLE 8.3—*Survival times for male beagles subjected to small daily x-ray exposures.*[a] *1000 kVp x rays of HVL 6 mm Pb. Target to skin distance 15.2 cm. Exposure rate, 0.006 to 0.06 R min*$^{-1}$ *in air during 10 minutes of each working day.*[b]

Daily exposure (R)	Weekly exposure (R)	Yearly exposure (R)	Av. lifespan exposure (R)	No. of dogs	Av. age at death (years)
0.00	0.0	0.0	0	20	13.0
0.06	0.3	15.6	190	20	13.8
0.12	0.6	31.2	360	10	13.2
0.60	3.0	156.0	1640	10	12.3

[a] Least square regression analysis on average age at death vs. average lifespan exposure, with the data from each control and irradiated group weighted in proportion to the number of animals each contained, indicated a life shortening ± standard error of 21 ± 17 days per 100 R of lifespan exposure. The indicated life shortening was not statistically significantly different from zero.

[b] From Casarett and Eddy (1968).

TABLE 8.4—*Survival times in female beagles after abrupt x-ray exposure*[a] *(Bilateral exposure, 250 kVp x rays of HVL 2.65 mm Cu. Target to midline 140 cm. Exposure rate, 8.5 R min*$^{-1}$ *in air midline.)*[b]

Total exposure (R)	Exposure pattern	Number of beagle dogs	Median survival times postirradiation (years)	
0	Sham irradiated	57		11.6
	25 R at 28-day intervals	22	11.0	
	25 R at 14-day intervals	25	10.0	
	25 R at 7-day intervals	20	11.3	
100	50 R at 28-day interval	21	10.6	10.5
	50 R at 14-day interval	21	9.8	
	50 R at 7-day interval	20	10.7	
	100 R single exposure	23	10.8	
	75 R at 28-day intervals	22	10.3	
	75 R at 14-day intervals	23	9.3	
	75 R at 7-day intervals	26	9.0	
300	150 R at 28-day interval	25	9.2	9.2
	150 R at 14-day interval	21	8.5	
	150 R at 7-day interval	23	8.7	
	300 R single exposure	11	10.4	

[a] Least squares regression analysis, with the data from each control and irradiated subgroup weighted by the number of dogs each contained, indicated a lifespan shortening ± standard error of 268 ± 46 days per 100 R on a linear scale.

[b] From Andersen and Rosenblatt (1969).

when delivered at high rates; and the ratio of effectiveness lies in the range indicated by data for the mouse (see Norris *et al.*, 1976). Precise statements about shapes of dose-response relationships are not warranted because of the relatively small sample sizes used.

In the case of man, the limited data available are consistent with

those for mice (NAS, 1972). With few exceptions, populations exposed to gamma rays at high total doses have shown an increased mortality rate. The only large groups exposed over a long-protracted period that have been studied so far are the British and U.S. radiologists in practice in the earlier part of the century. The former did not show evidence of life shortening, while the latter showed an excess of age-specific mortality as compared to ophthalmologists and otolaryngologists. The risk of death from all causes in the U.S. radiologists was increased by about 40 percent. The excess mortality cannot be attributed to cancer alone, since it persists after discounting all deaths from malignancy (Matanoski *et al.*, 1975a). The most suitable comparison group that received a single high-dose-rate exposure is represented by the survivors of the Nagasaki atomic bomb. In the period 1950–1972, the relative risk of death from all causes in those exposed to kermas of 200 or more rads was 1.24. Since the upper 90 percent confidence limit on this estimate is 1.43, it follows that the relative risks in the atomic-bomb survivors and the radiologists did not differ statistically. If we assume that the relative risks of death from all causes were the same, then the extent of the decrease in effectiveness by protraction of the exposure depends on the values assumed for total doses in the two groups. The Japanese in the highest kerma group received kermas of 200 rads or more. NAS-NRC (1972, p. 108) indicates that 138 survivors in the 1950–1970 study (or about 10 percent) in the above 200 rads group were estimated to exceed 600 rads. These survivors were assigned kermas of 600 rads. On this basis the average kerma for the group was 334 rads. If one uses the mean bone marrow dose to kerma ratio of 0.55 computed by Jones (1977) and neglects the small neutron component of kerma, one obtains a mean bone marrow dose of about 180 rads from gamma rays. The dose to the radiologists is not known. Braestrup (1957), using detailed knowledge of the x-ray equipment and the working habits of the radiologists, estimated their accumulated exposure at 2000 R, exposure in air (absorbed dose would be smaller). Lewis (1957) estimated the dose as between 100 and 1000 rads. Grahn (1970) estimated the mean bone marrow dose as lying between 1300 and 1600 rads from an interspecies comparison of life shortening by protracted exposure. Marinelli (1970) estimated the marrow dose at about 600 rads. If one assumes the dosage was about 1000 rads, then it follows that the protracted exposure was about ⅕ as effective as the single, brief exposure. One would have to assume that the dose was as low as 200 rads in order for the data to provide no evidence for any protraction effect.

Data are not adequate for the construction of dose-response curves for life shortening in man. Since much, if not all, of the life shortening

is due to the increased incidence of neoplasms, it is noteworthy that in the case of leukemia, for which the data are sufficient to give some confidence to detailed consideration of dose-response curves, the results are not consistent with the findings reported above for life shortening in mice. Neutrons (based on the data from Hiroshima) yield a linear relationship for all forms of leukemia combined; whereas gamma rays (Nagasaki) give a response somewhat more compatible with a quadratic function, the RBE for neutrons decreasing with increasing dose, as will be discussed in a subsequent report.

In assessing the effects of leukemia or other induced malignancies on the average life span of an irradiated population, account must be taken of the age-distribution of those affected. Although the degree to which radiation-induced cancer diminishes the average life expectancy would be a relevant parameter with which to assess the impact of radiation on a population, the data needed for such an assessment are not yet available on human populations. In any case, shortening of life span as an overall "integrator" of the impact of malignancy on a population has disadvantages as well as advantages. While it measures a parameter of vital interest to everyone, namely the degree to which the normal life span is compromised, it does not disclose what has happened to individuals of various ages. Thus, it is a valuable adjunct to, but cannot substitute for, age-specific incidence and mortality rates.

Summary of Effects on Life Span: Life expectancy is decreased by whole-body irradiation to a degree that varies in any given species with age at irradiation, dose, dose rate, and LET. The mechanisms of the effect and the extent to which it involves the induction of lesions other than neoplasms at a particular dose remain to be determined. In mice exposed to high-LET radiation, the degree of life shortening increases as an approximately linear function of the dose and is relatively independent of the dose rate. In fact, there is evidence that protraction may increase the amount of life shortening per rad of high-LET radiation above certain dose levels. For low-LET irradiation, mice show five-to-ten times less life shortening per unit of absorbed dose with protracted, as opposed to high-dose-rate exposure. The experimental dose-response data for low-LET radiation are consistent with the interpretation that the degree of life shortening varies as a polynomial function of the dose, a linear dose term predominating at low doses and low-dose rates and a squared dose term predominating at high doses and high-dose rates. Precise parameters of the dose-response relation appear to vary, however, under the influence of genetic, physiologic, and other variables, which affect the types, frequencies, severities, and age-distributions of the life shortening lesions in question.

9. Tumorigenesis in Experimental Laboratory Animals

Although a large amount of research has been directed toward the study of radiation carcinogenesis, there are few instances in which the influence of dose and dose rate on tumor induction have been analyzed over a sufficiently wide dose range to define adequately the shape of dose-response curve after low-LET radiation exposure and to assess the influence of dose rate on this dose-response relationship. The first part of this section will examine briefly the form of the dose-response curve for relatively high-dose-rate exposure, and the limitations of these data will be discussed. The second part will examine data on dose-rate effects.

9.1 Form of the Dose-Response Curve

9.1.1 *Leukemia in Mice*

Upton has shown that male RF mice are particularly sensitive to the induction of myeloid leukemia, and the dose-response relationship for the induction of myeloid leukemia in male RF mice has been examined over a wide range of x- or gamma-ray doses including those as low as 25 rads (Upton *et al.,* 1960, 1964, 1966, 1970). In these studies, over the dose range of 0–150 rads, the incidence appears to vary with the square of the dose, although the precise shape cannot be determined and a linear relationship cannot be excluded (Figure 9.1). Generalizations from these results are complicated since it has been shown that females are less sensitive to the induction of myeloid leukemia and that sensitivity to induction can also vary with a number of host factors, including genetic background, hormonal status, age, proliferative state of the bone marrow, and the condition of environment in which the animals are maintained (Upton *et al.,* 1964, 1966). For example, animals housed in conventional animal facilities seem to be most susceptible, while animals maintained in a germ-free or specific-pathogen-free environment show a reduced sensitivity to the

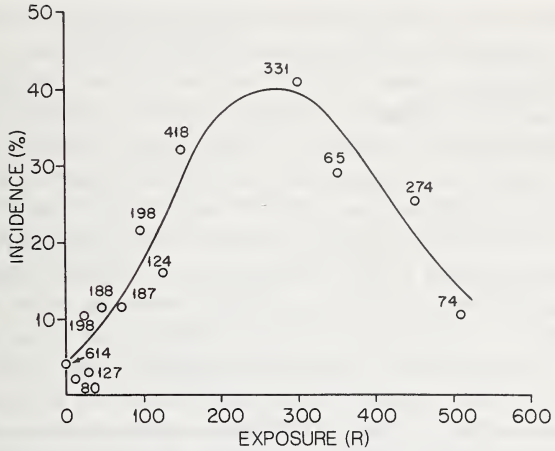

Fig. 9.1. Incidence of myeloid leukemia in male RF mice after x or γ irradiation at high-dose rate. The number of mice at each point are shown (From Upton *et al.,* 1964).

induction of myeloid leukemia but an increased sensitivity to the induction of thymic lymphoma (Upton *et al.,* 1964, 1966 and Walburg *et al.,* 1968). More recently, a dose-squared relationship for myeloid leukemia in male CBA mice was reported by Major and Mole (1978) although the dose range was quite limited.

Investigators have intensively studied the induction of thymic lymphoma after radiation exposure (Kaplan, 1964, 1967; Haran-Ghera, 1973). However, most of these studies have been concerned with modifying factors, the time course of the disease, or the sequence of events leading to its development rather than the dose-response relationship. Some early studies of Upton *et al.* (1966) and Upton (1968) have suggested that radiation was generally more effective per unit dose at intermediate dose levels than at low or high-dose levels, i.e., a dose-squared or linear, dose-squared relationship followed by a plateau was likely, but data were not available over a sufficiently wide dose range to define adequately the form of the response.

The dose-response relationship for the induction of thymic lymphoma in specific-pathogen-free RFM mice after ^{137}Cs gamma-ray doses as low as 10 rads has been reported by Ullrich and Storer (1978; 1979a) and by Ullrich *et al.* (1976). An examination of the form of the response indicated that no simple mathematical model could adequately describe the dose-response relationship over the entire dose range. Rather, a complex response was seen consisting of a component over the 0–25 rad range in which the incidence increased with the square of the dose followed by a second, linear component over the 50–300 rad range. Although the biological basis for the two-component

nature of the curve is unknown, the investigators have suggested that it may be a result of two different mechanisms of action. According to these investigators, over the 0–25 rad range the primary effect of radiation was the conversion of late-appearing reticular tissue neoplasms (reticulum cell sarcoma) to early ones (thymic lymphoma). This effect might be considered in the broad sense to be a form of acceleration. At higher doses (50–300 rads) new thymic lymphomas appeared to be induced as well. Because of the complex nature of the mechanisms involved in the development of thymic lymphoma and the complicated nature of the entire dose-response curve, only limited interpretation of these data is now possible. If it is assumed, as suggested by a number of studies (Kaplan, 1964; 1967), that the mechanism for the induction of thymic lymphoma involves killing of bone-marrow cells and lymphoid tissue, release of virus, and incorporation of virus into the target cells in the thymus, it is unlikely that a simple model based on biophysical interactions with molecules within a single cell would apply. Additional aspects related to the data on thymic lymphoma will be discussed in the section on dose rate.

9.1.2 *Ovarian Tumors in Mice*

A number of studies have shown that the incidence of ovarian tumors in the RF mouse is greatly increased by doses of 50 rads (Ullrich and Storer, 1978; Ullrich *et al.,* 1976; Upton *et al.,* 1970; Ullrich and Storer, 1979b). Details in other strains of mice are less well known, although a similar sensitivity has been shown for the BALB/c mouse (Yuhas, 1974). In fact, most studies suggest that the maximum tumor incidence in the RF and BALB/c mouse is produced by doses in the range of 50–100 rads. Data at doses below 50 rads are limited. The most extensive study on ovarian tumorigenesis in RFM mice has been reported by Ullrich and Storer (1978; 1979b) and Ullrich *et al.* (1976). In this study, over the dose range of 0 to 50 rads (including doses of 0, 10, 25, and 50 rads) linear, dose-squared, and threshold plus linear models could be rejected ($P < 0.01$) while linear-quadratic and threshold plus dose-squared models adequately described the relationship (Figure 9.2). At higher doses the dose response appeared to plateau. Although the linear-quadratic model adequately described the relationship, it should be pointed out that the slope of the linear portion of the linear quadratic was negative and in fact a zero slope was excluded at the 95 percent confidence level (−0.438 to −0.024). There is no apparent biological basis for a negative initial slope and the induction of expression of those tumors appears to require a certain

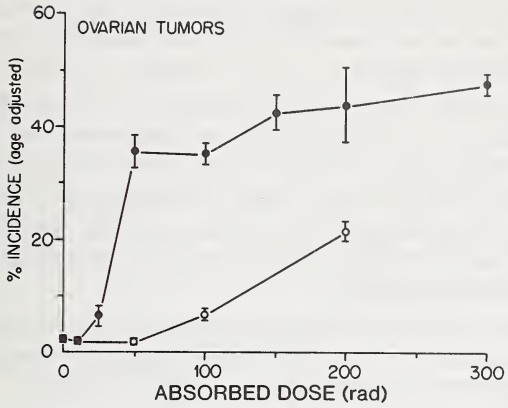

Fig. 9.2. Incidence of ovarian tumors in RFM mice after ^{137}Cs gamma-ray irradiation. 45 rad min^{-1} solid circle; 8.3 rad d^{-1} small open circle (From Ullrich and Storer, 1978).

degree of cell killing, which in turn results in a decreased level of estradiol production (impairment of organ function). This change is sufficient to cause increased secretion of gonadotrophins that ultimately results in an increased incidence of ovarian tumors (Fould, 1975). Thus, it is likely that this tumor may exhibit a threshold, a possibility that will be discussed further in the section on dose rate.

9.1.3 *Mammary Tumors*

The incidence of mammary tumors in irradiated rats and mice varies markedly, depending on the strain, type of tumor, and condition of irradiation (e.g., Shellabarger, 1976). The most extensive dose-incidence data have been derived from experimentation with Sprague-Dawley female rats, the great majority of which develop mammary tumors spontaneously after 15 months of age. In these animals, total body x-ray or ^{60}Co gamma-ray irradiation at 1–2 months of age advances the onset of tumors; and the incidence of total tumors scored within one year after exposure increases as a linear function of the exposure from 25–400 R with x rays (Bond *et al.,* 1960) and 16–250 R with ^{60}Co gamma rays (Shellabarger *et al.,* 1969).

A number of aspects of this system, however, complicate the interpretation of these data (Bond *et al.,* 1960, 1964; Cronkite *et al.,* 1960). The spectrum of tumor types is broad, including fibrosarcomas, fibroadenomas, and carcinomas. The dose-response relationship for the individual tumor types is less clear. In all of these studies, a cut-off period of approximately twelve months was used, because beyond that

point the control incidence begins to rise until near the end of the life span the total tumor incidence in control animals approaches that seen earlier in irradiated animals (i.e., the absolute incidence is increased minimally if at all). This situation raises the serious question as to whether radiation is accelerating the normal process or truly inducing tumors, i.e., what is the meaning of an "increased incidence" and of "dose-incidence" curves under these circumstances? The interpretation of the dose-response curve becomes unclear and interpretations of the data in terms of mechanisms of radiation-induced tumorigenesis must be made with caution.

Rats of other strains and other animals appear to be much less likely to develop mammary tumors after irradiation than female rats of the Sprague-Dawley strain (Ullrich *et al.*, 1976).

9.1.4 *Other Tumors*

There are few other tissues for which information on the dose-response relationship for tumors is sufficiently well characterized to examine its form. In the studies of Ullrich and Storer (1978; 1979b) the dose-response relationships for pituitary and Harderian-gland tumors after ^{137}Cs gamma-ray irradiation were examined for doses over the range of 0–300 rads, including some as low as 10 rads. Although the exact relationship differed for each tumor type, an analysis of the dose-response relationships for the induction of the pituitary tumors over the 0–300 rad range and Harderian-gland tumors over the 0–200 rad range (Figure 9.3) indicated that linear-quadratic models adequately fit the data in each case. It should be pointed out, however, that linearity could only be statistically excluded in the case of Harderian-gland tumors.

9.2 Influence of Dose Rate on Tumorigenesis

There have been relatively few instances in which the time-dose relationships for tumor induction after radiation exposure have been examined systematically with adequate attention to the control of other variables. At present, therefore, it is difficult to derive generalizations with respect to the influence of dose rate on the tumorigenic effectiveness of radiation. Inferences about the effects of dose rate are complicated by the many types of radiation effects that may contribute to the carcinogenic process, some operating at the cellular level, others at tissue, organ, or systemic levels. The role of these various effects in

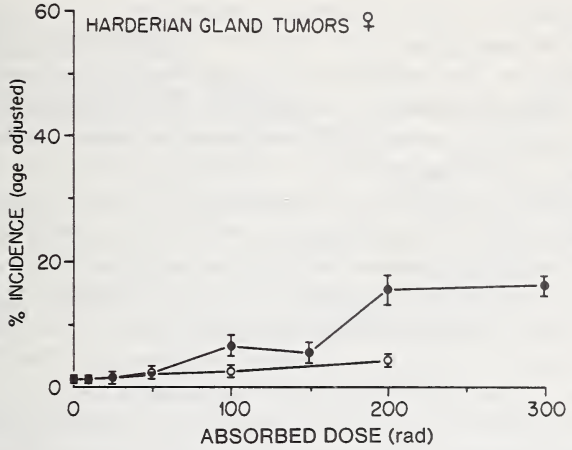

Fig. 9.3. Incidence of Harderian gland tumors in RFM mice after ^{137}Cs gamma-ray irradiation. 45 rad min^{-1} solid circle; 8.3 rad d^{-1} small open circle (From Ullrich and Storer, 1978).

the process of carcinogenesis may also differ. Some effects may play a role at the level of initiating events while others may be involved in events that control tumor expression. The influence of dose rate may vary from one contributory factor to another and for each of these factors it may vary with dose level, so that total dose and dose rate can influence not only the degree of effects produced, but also the nature of the effects on the target and interacting cell populations. In addition, the relative importance of the contributions made by the various initiating, promoting, and modifying mechanisms involved in the carcinogenic process may differ for different types of neoplasms. As a result, it is likely that the effect of dose rate may vary with the type of neoplasm in question, as well as with the dose and the combination of cells and tissues irradiated.

Since our knowledge of mechanisms remains incomplete, we are dependent, for the most part, on empirical analysis of the available information. For the present analysis a distinction must be made between studies of protraction and of dose rate and between these studies and studies that utilize fractionated exposure.

Many of the fractionation studies have used relatively high doses per fraction, and at the present time the applicability of such studies to dose-rate effects is not known. Thus, although fractionation studies can be useful for the understanding of carcinogenic mechanisms and eventually for understanding the basis for dose-rate effects, the relative importance of dose per fraction, fraction interval, total dose, and dose rate are poorly understood for most tumors.

For purposes of this discussion, protraction is used to describe exposures that are spread over a period of the life span during which susceptibility to the induction of tumors may change. Studies of duration-of-life irradiation are an example. Because there is no adjustment for changes in susceptibility with age for tumor induction or, in some cases, age adjustments for competing risks, these protraction studies cannot be used for the assessment of true dose-rate effects alone. Protraction of the period over which the animal is irradiated may alter the effects because of: 1) true dose-rate effects and 2) age-dependent changes in susceptibility to tumor induction. Furthermore, while all of the radiation dose incurred over most of the lifetime may have an effect, the radiation incurred at the end of the lifespan can play no part in the induction of those tumors that require considerable time between tumor induction and detection. Thus, the above limitations notwithstanding, the following data are summarized as our major sources of cogent evidence on the influence of dose rate on radiation carcinogenesis.

9.2.1 *Leukemia in Mice*

Among the first experiments to explore systematically the time-dose relationships in leukemogenesis were those of Kaplan and Brown (1952) which indicated that the lymphoid tumor-inducing effectiveness of high doses of whole body irradiation could be either increased or decreased by high-dose-rate fractionation, depending upon the size and periodicity of exposures. In all instances, the dose per fraction was relatively high (Figure 9.4). From further studies by Kaplan (1964) it became apparent that the mechanisms involved in the induction of murine thymic lymphoma were complex and the importance of size and periodicity of the radiation exposure was to maximize the probability of interaction of the various factors involved. Although these experiments have provided important mechanistic information, they were not intended to address the question of low-dose-rate effects, and attempts to derive information on dose rate from these studies would be unwarranted. The difficulties involved in attempting to relate information obtained from studies using high-dose schemes to dose-rate effects is pointed out in studies by Upton *et al.* (1964) on myeloid leukemia induction. In these studies, fractionation of doses into 2–3 exposures of 75–150 rads at high-dose rates gave similar results to those obtained after single exposures while, as discussed below, low-dose-rate exposures were significantly less effective.

On protraction of gamma irradiation, a reduced incidence of lym-

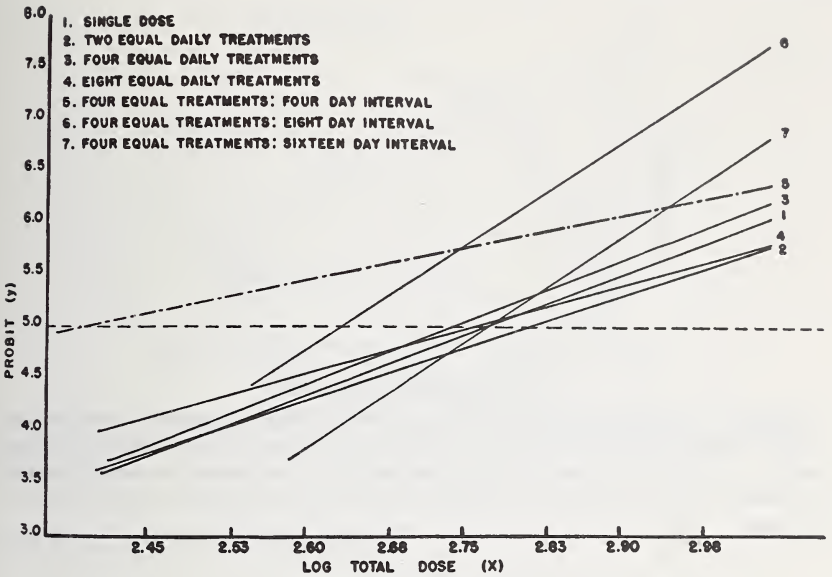

Fig. 9.4. Comparative probit-regression lines for lymphoma incidence in irradiated C57 black mice. The 50 percent level (Y = 5.0) is indicated by a horizontal dashed line (From Kaplan and Brown, 1952).

phoma per unit dose with decreasing dose rate over the range of 5–32 R d^{-1} was observed by Lesher *et al.* (1965) in mice under exposure for the duration of life. However, interpretation of these data is complicated since no adjustment for competing risks due to different distributions of ages at death among the various treatment groups was attempted. A comparison of single and duration-of-life gamma-ray exposures reported by Grahn *et al.* (1972), in which mortality ratios were used to adjust for competing risks, indicated that single doses delivered at 2–20 R min^{-1} gave an excess risk of leukemia mortality that was significantly greater than for comparable levels of accumulated dose under low intensity daily irradiation (5–32 R d^{-1}).

Upton *et al.* (1970) observed that the yield of myeloid leukemia per unit absorbed dose of x rays was reduced under conditions of continuous exposure for 23 hours daily at low-dose rates compared to the yield at similar doses delivered at high-dose rates (Figure 9.5). The effect could generally be characterized as a diminution of the second-order component observed at high-dose rates resulting in a more linear response at the lower dose rate. Susceptibility to the induction of myeloid leukemia has not been found to depend on age over the intervals used for the chronic radiation exposures. Thus, the differences appear to be true dose-rate effects. Because of the many known host

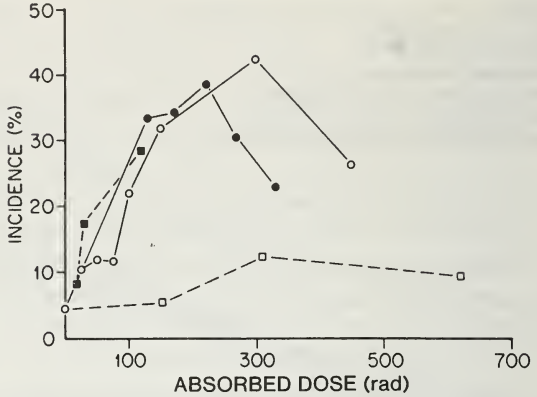

Fig. 9.5. Incidence of myeloid leukemia in RF male mice. Shaded symbols denote results obtained with fast neutron irradiation; open symbols denote results obtained with x rays. Solid lines denote results obtained with acute (single) exposures; dashed lines denote results obtained with chronic (23-hour, daily) exposures (From Upton *et al.*, 1970).

factors involved in the expression of myeloid leukemias (Upton *et al.*, 1964; 1966), it is not clear from the data presently available whether the basis for the observed dose-rate effects is related to influences on factors involved in tumor expression (e.g., hormones, cell turnover) or in fact to dose-rate effects on initial events.

Experiments comparing the effects of gamma irradiation delivered at 45 rad min^{-1} and 8.3 rad d^{-1} on the incidence of thymic lymphoma indicated that the low-dose-rate gamma-ray exposure was less effective at all doses tested when compared to similar doses delivered at the high-dose rate (Ullrich and Storer, 1978; 1979c). As with the experiments of Upton *et al.* (1970), changes in age susceptibility could be excluded and the difference seemed to be due primarily to dose-rate effects. Surprisingly, even at the lower dose rate (8.3 rad d^{-1}), the relationship between dose and the induction of thymic lymphoma was best described by a linear-quadratic model with a very shallow initial slope and linearity could be rejected ($P < 0.001$) (Figure 9.6). These data appear to be inconsistent with predictions based on the biophysical theory of dual-radiation action (see Sections 2, 3). However, as discussed earlier in this section, it may be that because of the mechanism of induction a simple biophysical model based upon actions within a single cell need not apply and that, rather, the induction or expression of thymic lymphoma is highly dependent on cell killing and the target cell-viral interactions that result. The data on low-dose-rate effects would seem to be consistent with such an hypothesis.

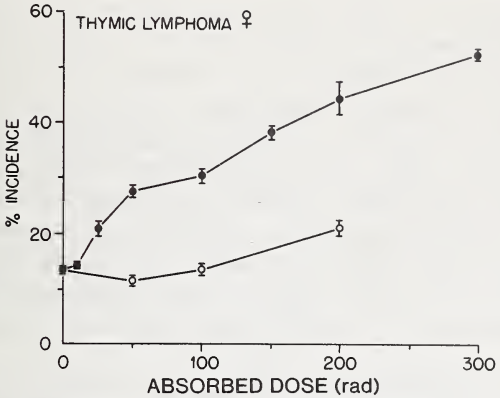

Fig. 9.6. Incidence of thymic lymphoma in female RFM mice after ^{137}Cs gamma-ray irradiation. 45 rad min^{-1} solid circle; 8.3 rad d^{-1} small open circle (From Ullrich and Storer, 1978).

9.2.2 *Ovarian Tumors in Mice*

It has been observed repeatedly that the induction of ovarian tumors in gamma-irradiated mice is dependent on the dose rate (Ullrich and Storer, 1978; Yuhas, 1974; Upton *et al.,* 1970). Interpretation of the data is complicated by a decrease with age in the susceptibility of the mouse ovary to tumorigenesis during the exposure period. Therefore, the results obtained represent protraction effects consisting of dose-rate effects and effects related to decreasing susceptibility to tumor induction during exposure. This protraction effect has been analyzed by Yuhas (1974) in connection with the influence of dose rate itself. The results in BALB/c female mice given total doses of 49, 98, 196, or 392 rads of gamma radiation at rates of 1.75, 3.5, 7, 14, 28, 56, or 112 rads per day were described by the following equation:

$$\text{Excess incidence of mice with ovarian tumors} = KD^2\,T^{-0.69} \quad (9.1)$$

where D = total absorbed dose (rad) and T = exposure time in days. Since, however, acute exposures of mice at various ages indicated that about one-third of the overall effect was attributable to age-dependent loss of susceptibility to ovarian tumorigenesis (Figure 9.7), the corrected relationship between tumor yield and exposure time, or dose rate, was given by the formula:

$$\text{Excess incidence of mice with tumors} = KD^2\,T^{-0.46} \quad (9.2)$$

The above expression (Equation 9.2) indicates that the yield of ovarian tumors decreases approximately with the square root of the exposure time, while increasing with the square of the dose. The basis for the

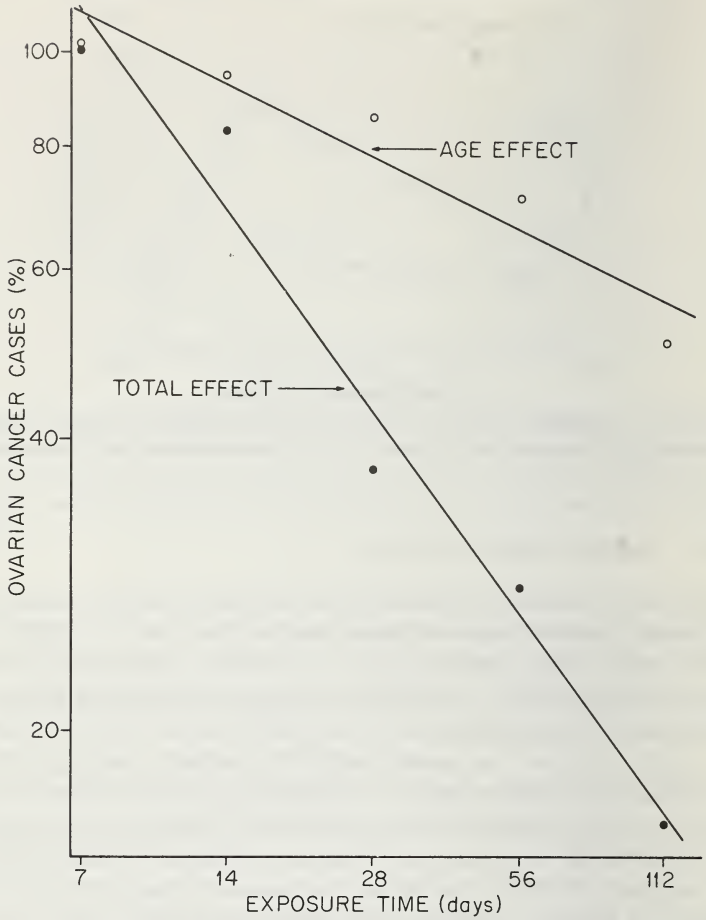

Fig. 9.7. Effect of exposure time (dose rate) on the induction of ovarian tumors in BALB/c mice (From Yuhas, 1974).

observed dependency on exposure time or dose rate remains to be elucidated fully. However, since the sequence of events leading to induction of the tumors is believed to start with the killing of oocytes (Upton, 1961; Upton *et al.*, 1960), a reduction of tumorigenesis with low-dose-rate irradiation may be correlated, at least in part, with the reduced cell killing effectiveness of gamma irradiation for oocytes at low-dose rates. Relative to the dependency of ovarian tumorigenesis on cell killing, recently-published experiments (Ullrich and Storer, 1978; 1979c) comparing the form of the dose response for ovarian tumorigenesis after ^{137}Cs gamma rays delivered at 45 rad min^{-1} and 8.3

rad d^{-1} in RFM mice indicated that the form of the dose response at both the higher and the lower dose rate could be described by a linear-quadratic model with a negative initial slope or by threshold models. For both dose rates a linear relationship with dose could be rejected. Following the threshold, the incidence of ovarian tumors increased with the square of the dose after high-dose rates; while after low-dose rate irradiation the size of the threshold was increased and the relationship between tumor incidence and dose following the threshold was more linear (Figure 9.2). These data suggest that ovarian tumorigenesis after irradiation is, in fact, highly dependent upon achieving a certain level of cell killing before induction or expression can take place.

Although ostensibly at variance with the foregoing data on decreased effectiveness at reduced dose rates, it is not surprising that irradiation at low-dose rates (1.45 rad h^{-1}) has appeared (Nowell and Cole, 1965) to increase the tumorigenic effectiveness of gamma rays for the mouse ovary after very high total doses (618–2408 rads). These doses far exceed the dose necessary to produce maximum effect under conditions of high-dose-rate exposure and are in the region of the dose-response curve where the yield is greatly reduced at high-dose rates. Under these conditions, the effects of protraction are presumably correlated to a large extent with the sparing of potential tumor-forming cells, which would be injured too severely by the large doses in question delivered at high-dose rates to remain capable of expressing their oncogenic potential. Also, in the case of tumors occurring late in life, high single doses that result in marked life shortening will not allow time for expression of tumors.

9.2.3 *Lung Tumor Induction in Various Species of Animals*

Relatively little useful information is available regarding the influence of dose rate on tumor induction after radiation exposure of the lung. In studies (Ullrich and Storer, 1978; 1979c) comparing the tumorigenic effects of whole-body gamma irradiation delivered at 45 rad min^{-1} or 8.3 rad d^{-1}, the low-dose rate radiation exposure was observed to be less effective in inducing adenocarcinomas of the lung in BALB/c mice than were similar doses delivered at the high-dose rate (Figure 9.8). Since, in these studies, no changes in sensitivity with age during the exposure were observed and the data were adjusted for differences in distribution of ages at death among the various treatment groups, it appears that differences observed can be attributed to a decreased tumorigenic effectiveness with decreased dose rates. Although a dose-

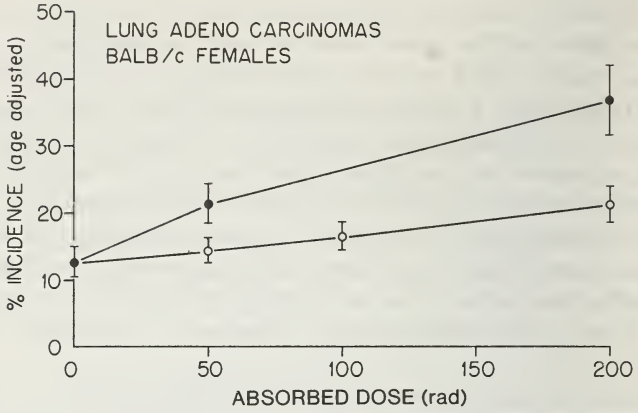

Fig. 9.8. Incidence of lung adenocarcinomas in female BALB/c mice after ^{137}Cs gamma-ray irradiation: 45 rad min^{-1} (solid circle); 8.3 rad d^{-1} (small open circle) (From Ullrich and Storer, 1979c).

rate effect could be derived by a comparison of the slopes of the high- and low-dose-rate-response curves, these data were not adequate to define the form of the curves or to examine the importance of total dose on dose-rate effects.

Interpretation of these dose-rate data and the basis for the observed dose-rate effects are further complicated, however, by a study on BALB/c lung adenocarcinoma recently reported by Yuhas (1979). In this study, when doses of 196 rads were delivered at dose rates varying from 1.75 to 112 rad d^{-1}, the incidence of lung tumors increased above that observed at the highest dose rate with decreasing dose rate down to rates of 14 rad d^{-1}. At still lower dose rates, the lung tumor incidence declined and at 1.75 and 3.5 rad d^{-1} was lower than that observed after high-dose-rate irradiation.

9.2.4 *Breast Tumors in Rats and Mice*

Irradiation of the breast with either x rays or gamma rays at an age of 1–2 months advanced the onset of mammary tumors in the Sprague-Dawley rat such that the incidence scored within one year after exposure increases as a linear function of the exposure from 25–400 R (Bond *et al.,* 1960) for x rays and from 16–200 R (Shellabarger *et al.,* 1969) for ^{60}Co gamma rays (see Section 9.1.3 for difficulties in interpreting incidence and curve shapes under these circumstances). Although the dose response for mammary tumorigenesis in the Sprague-Dawley rat after acute irradiation is reasonably well defined (see Section 9.1.3), there is very little information on the influence of dose

rate. In studies of a preliminary nature (Shellabarger and Brown, 1972), after protracted ^{60}Co gamma irradiation to a cumulative exposure of 88 R or 265 R, accumulated at a rate of 0.03 R min^{-1}, the total yield of mammary neoplasias (adenocarcinomas and fibroadenomas) was observed to be similar per unit dose to that after gamma irradiation delivered at a rate of 10 R min^{-1}. By examining adenocarcinomas and fibroadenomas separately, a small but significant dose-rate sparing effect was found for the induction of mammary adenocarcinomas at a total exposure of 265 R but no significant sparing effect was observed for adenocarcinomas at the lower dose (a smaller effect would be expected at the lower doses). No sparing was observed for the induction of the benign fibroadenomas. When the number of tumors per rat was calculated, a sparing effect was also observed, probably as a result of the dose-rate effect on adenocarcinomas. On fractionation of 400–500 R of x rays into as many as 32 exposures delivered over a 16-week period, there was no apparent change in the total tumor incidence, possibly because the total dose exceeded the level at which the response reaches maximum with single-exposure irradiation (Shellabarger *et al.*, 1962; 1966).

Although dose-response relationships have been less well characterized in other animals, data on the influence of dose and dose rate on the induction of mammary adenocarcinomas have been reported in BALB/c mice after whole-body gamma-ray irradiation (Ullrich and Storer, 1978; 1979c) (Figure 9.9). Although the data were not adequate to define the form of the dose response at the high- or the lower-dose rate, they were sufficient to compare the effectiveness of ^{137}Cs gamma

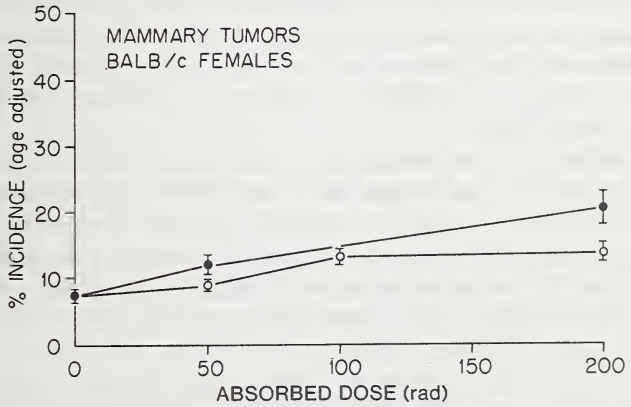

Fig. 9.9. Incidence of mammary tumors in female BALB/c mice after ^{137}Cs gamma-ray irradiation: 45 rad min^{-1} (solid circle); 8.3 rad d^{-1} (small open circle) (From Ullrich and Storer, 1979c).

irradiation delivered at 45 rad min^{-1} and 8.3 rad d^{-1}. The slopes of the lines were obtained by using a weighted linear regression for the two dose rates on the assumption that the difference in slope was a reflection of a difference in effectiveness. A comparison of these linear slope constants suggested a dose rate effectiveness factor of 1.9, i.e., the high-dose-rate exposure was 1.9 times as effective as the lower-dose rate. In comparison with the other tumors analyzed in this study, this was the smallest reduction in effect with decreased dose rate observed. Taken together, the studies in the Sprague-Dawley rat and the BALB/c mouse would suggest that the influence of dose rate on mammary tumor induction may be less than that observed for most other tumors.

9.2.5 *Other Tumors*

In addition to the analysis of dose-rate effects on the induction of thymic lymphoma, ovarian tumors, lung tumors, and mammary tumors already discussed, the studies of Ullrich and Storer (1978; 1979c) also examined the influence of dose rate on the induction of pituitary and Harderian gland tumors (Figure 9.3) in RFM mice. An analysis of the dose-response relationships for tumor induction after high- and low-dose rate gamma irradiation for these tumors indicated a linear quadratic response for the high-dose rate and a linear response for the low-dose rate. In each case, although the exact mathematical relationship varied for each tumor type, the linear component was similar for both the high- and low-dose rate, a result suggesting that the primary influence of dose rate was to diminish the dose-squared component and thereby to result in a more linear response. It should be emphasized, however, that the data were not sufficient to examine rigorously whether the linear slopes were equal under high and low dose rate exposure conditions.

Information on other tumors from other studies is less well defined. In CBA mice, a nominal absorbed dose of 6000 or 12,000 rads of beta radiation fractionated over an exposure period of up to three months was only slightly less effective in inducing tumors of the dermis than when delivered in a single exposure (Hulse and Mole, 1969). The same doses induced a higher incidence of epidermal tumors when fractionated into four monthly exposures than when delivered in a single exposure or in 20 daily exposures (Figure 9.10). However, these studies are complicated by problems with dosimetry and by the fact that the doses were fractionated rather than delivered at a low-dose rate so that intrepretation of the results as they relate to dose-rate effects is difficult. In CD rats (Burns *et al.,* 1975), a single acute dose of electrons

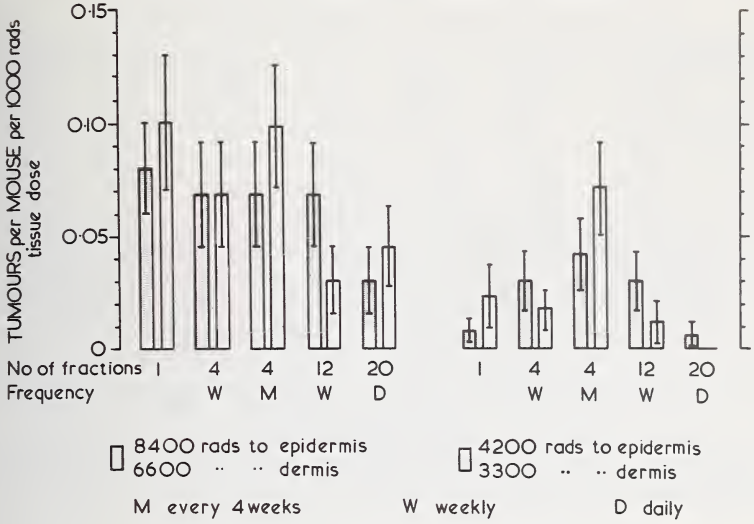

Fig. 9.10. The yield of dermal and epidermal tumors after single or fractionated exposures to beta particles. The yield is given as tumors per mouse per 1000 rads tissue dose (see text). The standard errors were calculated by assuming a Poisson distribution of tumors. The shaded columns represent data from mice given a total nominal air dose of 12,000 rads (average tissue doses; 8400 rads to the epidermis and 6600 rads to the dermis) and the unshaded columns those given a nominal 600 rads (average tissue doses; 4200 rads to the epidermis and 3300 rads to the dermis). M means one exposure every 4 weeks, W every 7 days, and D daily 5 days a week. (The authors, Hulse and Mole, 1969, note that remeasurement of the radiation source has shown that the doses should be increased by a factor of 2.17.) (From Hulse and Mole, 1969).

is about 50 percent more effective in inducing skin (hair follicle) tumors than the same dose delivered in two equal fractions 24 hours apart, as judged by the separation between the two dose-incidence curves (Figure 9.11). These results are similar to those obtained previously when the two fractions were separated by 31 days and suggest that most of the effect of fractionation occurred within the first 24 hours (Burns *et al.*, 1975; 1973). These results are consistent with the interpretation that recovery from the initial dose has occurred during this time interval. Although these studies are not directly applicable to dose-rate effects, the evidence for recovery from carcinogenic effects during split-dose exposures provided by these studies would imply that a reduced effect with decreased dose rate would be expected.

9.2.6 *Tumorigenesis from Internal Emitters*

In the following, only those data on internal emitters considered to have direct relevance to dose-rate dependence of low-LET radiation for carcinogenesis are included.

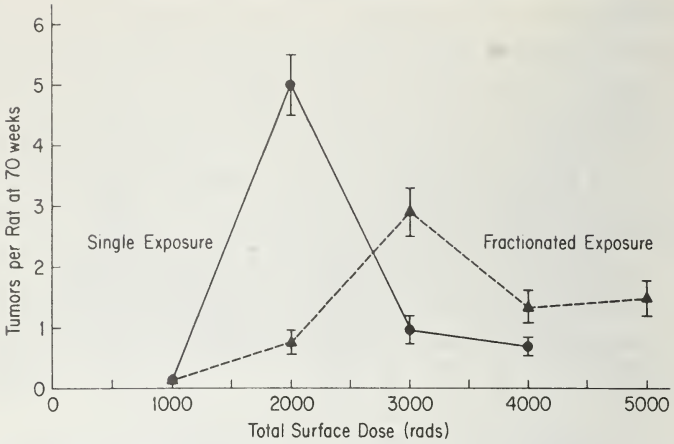

Fig. 9.11. Effect of fractionation on frequency of skin (hair follicle) tumors in CD rats (From Burns *et al.*, 1975).

Differences frequently exist between external and internal irradiation. External irradiation by x rays or gamma rays usually exposes the whole body, while internally-deposited emitters frequently give nonuniform irradiation to specific organs. External irradiation is often brief and at high-dose rates, whereas internal irradiation can be continuous, but at a changing dose rate due to radionuclide decay, excretion, and redistribution within the body. In addition, most of the internal emitter studies were not specifically designed to intercompare effects at high- and low-dose rates. These limitations severely restrict the number of reliable comparisons that can be made from existing data on internal emitters.

Bone tumors in various species of experimental animals. In mice (Finkel *et al.*, 1959; Finkel and Biskis, 1968), rats (Moskalev *et al.*, 1969), and dogs (Mays and Lloyd, 1972) the incidence of osteosarcomas per unit absorbed dose from long-lived bone-seeking beta emitters has been observed to be lower at average skeletal doses below 2000–4000 rads and at dose rates below 20 rads per day than at higher doses and higher dose rates (Mays and Lloyd, 1972). The data for mice, which enable comparison of the effects of similar skeletal doses accumulated at different dose rates, reveal that beta irradiation from ^{90}Y accumulated at dose rates of 32–127 rads per day (Table 9.1) was about 10–20 times more effective than that from ^{90}Sr accumulated at dose rates of 0.2–15 rads per day (Table 9.2).

Thyroid tumors in the rat. Comparison of the tumorigenic effects of x rays and internally-deposited ^{131}I on the rat thyroid gland prompted

TABLE 9.1—*Osteosarcomas in ^{90}Y-treated CF1 female mice*[a]

Initial injection (μCi kg^{-1})	Total injections (μCi kg^{-1})	Rad d^{-1} during 1st 100 h	Total dose (rad)	Number of mice	Mortality at 886 days (%)	Mice with osteosarcomas	
						(No.)	(%)
1000	2500	127	1100	30	100	4	13.3
500	1250	63	550	60	98.3	5	8.3
250	625	32	275	120	93.3	8	6.7
0	0	0	0	120	95.0	2	1.7

[a] After the initial injection of ^{90}Y, the mice were re-injected, each time with 30 percent of the initial activity, at 11, 30, 52, 76, and 100 hours after the 1st injection (Finkel and Biskis, 1968). The average skeletal dose was calculated assuming that: 75 percent of the injected ^{90}Y atoms decay in the skeleton (ICRP, 1960), the mouse skeleton is 7.5 percent of body weight, the half-life of ^{90}Y is 64 hours, the average energy per beta-particle is 0.93 MeV, and 24 percent of this energy is absorbed within the mouse skeleton (Parmley *et al.*, 1962). The dose rate during the injection period was averaged over the first 100 hours. These data are compatible with a linear slope of 1.36 percent incidence per 100 rad starting at the control incidence of 1.7 percent at zero dose. The least squares fit is 1.00 ± 0.14 S.D. percent incidence per 100 rad; starting at 2.70 percent incidence at zero dose.

Doniach (1963) to conclude that 1000 rads of x radiation is roughly equivalent in tumorigenecity to 10,000 rads delivered by ^{131}I. Two factors were mentioned as possible explanations for the higher effectiveness of the x rays: 1) spatial differences in dose distribution within the gland; and 2) temporal differences in dose rate, the rate of irradiation from x rays being many times higher than that from ^{131}I. Related to the difference in effectiveness of x rays and ^{131}I reported by Doniach (1963) are the studies of Greig *et al.* (1970). In these studies, cell survival curves were obtained by using the dose dependent decrease in response of thyroid glands to goiterogenic stimulation after irradiation to estimate cell survival. From these studies dose values for x rays and ^{131}I of 450 and 5500 rads, respectively, were obtained for equal levels of effect. Because of the range of ^{131}I beta irradiation and the kinetics of iodine metabolism, Greig *et al.* (1970) concluded that it was unlikely that inhomogeneities in dose distribution could account for these differences and therefore the major factor accounting for the observed effect was dose rate. Section 10.3 considers the human internal emitter data.

Lung tumors in various species of experimental animals. Data on pulmonary carcinogenesis after exposure to beta radiation in rats through the use of tracheobronchial implants or intratracheal instillations are available from studies of Laskin *et al.* (1970), Cember (1964), and Warren and Gates (1968); and from inhalation studies in dogs (Jones *et al.*, 1974; McClellan *et al.*, 1976). However, interpreta-

TABLE 9.2—*Osteosarcomas in ^{90}Sr-treated CF1 female mice*[a]

(Bone sarcoma mice)						
Injected (μCi ^{90}Sr kg^{-1})	Dose rate during 1st 100 hours (rad d^{-1})	Median days injection to death	Average skeletal dose (rad) to 140 days before death	Mice surviving at least 150 days	Mice with sarcoma	
					(no.)	(%)
2200	383	216	12000	26	19	73.1
880	153	260	6630	45	41	91.1
440	76.6	440	6300	42	34	81.0
200	34.8	510	3310	59	8	13.6
88	15.3	760	2090	74	2	2.7
44	7.66	640	900	83	3	3.6
8.9	1.55	—	172[b]	104	0	0
4.9	0.78	600	87	119	2	1.7
1.3	0.23	630	26	148	2	1.4
0	0	550	0	149	2	1.3

[a] An equilibrium mixture of ^{90}Sr and its daughter ^{90}Y was injected intravenously into CF1 female mice at 70 days of age (Finkel *et al.*, 1959). Subsequent activity of ^{90}Y was maintained by decay of the retained ^{90}Sr within the body. Average skeletal dose was calculated (Mays and Lloyd, 1972) up to the estimated start of tumor growth, which was assumed to average 140 days before death. Most of the dose was from ^{90}Y (average beta-energy = 0.93 MeV) rather than its parent ^{90}Sr (average beta-energy = 0.20 MeV). The early dose rate was averaged over the first 100 hours for comparison with values in the pure ^{90}Y experiment (Table 9.1). The incidence of radiogenic osteosarcomas is well represented up to 2090 rads by the fitted linear relationship of 0.07 percent incidence per 100 rad starting at the control incidence of 1.3 percent at zero dose. The least squares fit is 0.09 ± 0.06 S.D. percent incidence per 100 rads, starting from 1.27 percent at zero dose.

[b] Dose for mice treated with 8.9 μCi ^{90}Sr kg^{-1} was calculated at 600-140 = 460 days.

tion of the studies in rats is complicated by the trauma associated with the surgical manipulations and the non-uniform radiation dose distributions associated with the techniques used for exposure. The studies in both rats and dogs are further complicated by the extremely high doses required to produce significant tumor incidence. Because of the high doses used, studies on dose-rate effects are difficult to interpret, since with these doses animals exposed at high-dose rates would not be expected to survive long enough to be at risk for the development of primary lung tumors. As a result, such studies could be misinterpreted as indicating an enhanced tumorigenic effectiveness with protracted irradiation. In the studies of Laskin *et al.* (1970), in which the question of dose rate has been addressed using tracheobronchial implants, early death was not a complicating factor. However, in these studies the lowest exposure rates used were still several hundred rad per day. Because of all of these complicating factors, these studies on lung tumor incidence are of little use in approaching the problem of effects at low-dose rate.

Summary. In summary, internal emitters and external radiations show the same pattern of dose-rate effectiveness for low-LET radiation.

9.2.7 *Discussion*

Although the precise steps in the radiation-induced carcinogenic process are not understood, it is clear that different cancers can arise from different sequences of events. For some tumors the mechanism of carcinogenesis appears to be mainly a result of direct effects on the target cell, perhaps involving one or more mutations. While in many instances induction may occur through such direct effects, the expression of the tumor can be influenced by a variety of host factors, including endocrine status, competence of the immune system, and kinetics of target and interacting cell populations. The relative influence of these factors on the form of the dose-response relationship for most tumors is largely unknown.

In other tumors abscopal effects either predominate or play a major role in the initiation and expression of the tumors. Some of the hormone moderated tumors would fall into this class. For instance, in the case of ovarian tumors in mice, sterilization or sufficient oocyte killing to alter the ovary-pituitary axis results in elevated gonadotrophin hormone levels that eventually lead to neoplastic growth of one or more types of cells in the ovary. As pointed out, cell killing also appears to play a major role in the events that lead to the development of thymic lymphoma.

Some authors have attempted to describe the dose response for tumorigenesis with an expression that has both a linear and a quadratic component. Such a model may fit the data for tumors induced entirely by direct effects, but it is unlikely that the complex interactions involved in tumor induction or expression by abscopal effects are adequately described by such a simple model. For the initial physicochemical events leading to mutation or cell killing, the assumption that no threshold exists may or may not be reasonable. However, tumor induction involving a sequence of events in more than one tissue and a marked depression of some specific cell system or other mechanisms, including the possibility of a threshold, cannot be dismissed.

The results from experimental systems reported here indicate that the dose-response curves for tumor induction in various tissues cannot be described by a single model. Furthermore, although the understanding of the mechanisms involved in the induction of tumors in different cell systems is incomplete, it is clear that a variety of mechanisms is involved. As a result, the basis for any observed dose-rate effects may

range from influences of dose rate on events at the cellular level to influences on mechanisms influencing tumor expression rather than induction. Unfortunately, there is neither a complete nor a quantitative understanding of these mechanisms and their relative influences in any of the tumor types examined and, therefore, description of the dose-response relationships and dose-rate effects must be empirical.

For mammary tumors in Sprague-Dawley rats the dose response appears to be linear. In this instance, a dose-rate effect only for adenocarcinomas was observed. Although the data are not sufficient to determine the dose response in other strains or species, in general the influence of dose rate seems to be least for the induction of mammary tumors. For tumors such as thymic lymphoma or ovarian tumors in mice, which appear from their proposed mechanisms of induction to be highly dependent on cell killing, the response is more complex and relatively large dose-rate effects were observed. For those tumor systems such as Harderian gland and pituitary, in which dose-response curves for high doses can be described by linear-quadratic models, the form of the dose response for low-dose-rate exposures is more nearly linear with the linear components being similar for both the high- and low-dose-rate dose-response curves. In these instances the primary effect of reduced dose rate seems to be a reduction of effect in the intermediate region of the dose-response curve that diminishes the second-order component; and the result is a more nearly linear response. With fractionation, in contrast to protraction, the yield of neoplasms for a given dose of low-LET radiation at high-dose rate may either be decreased or in some instances be increased, depending on the magnitude and timing of successive exposures, the total dose, and the tumor type. In many instances, such enhancing effects of fractionation on carcinogenesis can be attributed to the sparing of cells that would otherwise be incapable of proliferation if exposed to the same dose in a single treatment. These and other cytotoxic effects of radiation greatly complicate the interpretation of dose-incidence curves and presumably contribute to their tendency to plateau and turn downward at high doses, where protraction may paradoxically cause an apparent reverse type of dose-rate effect.

Despite the complexities of experimental tumor studies and the lack of understanding of the types of mechanisms involved, in every well-executed experiment the tumorigenic effectiveness per rad of low-LET radiation tends to decrease with decreasing dose rate. For some tumor types the difference may be small or may appear only with very low-dose rates, while for others the dose-rate effects may be large. It is also apparent that the types of dose-response relationships for tumor

TABLE 9.3—*Dose-rate effectiveness factors for available experimental data*[a]

Animal data	$\alpha_{1.}$	α_{Ex}	DREF[b]
1. Decrease in mean survival time in RFM female mice (Ullrich and Storer, 1978; Storer *et al.*, 1978) (45 rad min^{-1} vs 8.3 rad d^{-1})	−0.767 (0–200)[c,d]	−0.35 (0–200)[c,d]	2.1
2. Life shortening in BALB/c female mice (Ullrich and Storer, 1978; Storer *et al.*, 1978) (45 rad min^{-1} vs 8.3 rad d^{-1})	−0.509 (0–200)[c,d]	−0.258 (0–200)[c,d]	2.0
3. Myeloid leukemia in RF male mice (Upton *et al.*, 1970) (80 rad min^{-1} vs 0.004-0.06 rad min^{-1})	0.14 (0–300)	0.021 (0–329)	6.7
4. Myeloid leukemia in RF female mice (Upton *et al.*, 1970) (7 rad min^{-1} vs 0.0004-0.07 rad min^{-1})	0.09[e]	0.04[e]	2.3
5. Thymic lymphoma in RFM female mice (Ullrich and Storer, 1978; 1979b) (45 rad min^{-1} vs 8.3 rad d^{-1})	0.135 (0–300)[c]	0.021 (0–200)[c]	6.4
6a. Ovarian tumors in RFM mice (Ullrich and Storer, 1978; 1979b) (45 rad min^{-1} vs 8.3 rad d^{-1})	0.39 (0–50)[c]	0.085 (0–200)[c]	4.6
b. Ovarian tumors in BALB/c mice (45 rad min^{-1} vs 8.3 rad d^{-1})	1.2 (0–50)[c]	0.18 (0–200)[c]	6.7
7. Thyroid tumors in rats (Doniach, 1963) (150 rad min^{-1} vs 1 rad min^{-1})	Single dose comparison		10
8. Mammary tumors in Sprague-Dawley female rats (Shellabarger and Brown, 1972) (10 rad min^{-1} vs 0.3 rad min^{-1})			
a. percent mammary neoplasms (includes benign)	.16	.16	1.1
b. percent adenocarcinomas only	.15	.034	4
c. neoplasms/rat	.004 (0–265)[c]	.002 (0–265)[c]	2
9. Pituitary tumors in RFM (Ullrich and Storer, 1978; 1979b) (45 rad min^{-1} vs 8.3 rad d^{-1})	0.042 (0–300)[c]	0.0072 (0–200)[c]	5.4
10. Harderian gland in RFM (Ullrich and Storer, 1978; 1979b) (45 rad min^{-1} vs 8.3 rad d^{-1})	0.049 (0–300)[c]	0.015 (0–200)[c]	3.3
11. Lung adenocarcinomas in BALB/c (Ullrich and Storer, 1978; 1979b) (45 rad min^{-1} vs 8.3 rad d^{-1})	0.12 (0–200)[c]	0.043 (0–200)[c]	2.8
12. Mammary adenocarcinomas in BALB/c (Ullrich and Storer, 1978; 1979b) (45 rad min^{-1} vs 8.3 rad d^{-1})	0.067 (0–200)[c]	0.035 (0–200)[c]	1.9

[a] The linear regression coefficients (α_{Ex} and α_L) and the DREF values in this table were based on calculations of R. L. Ullrich. Similar linear regression coefficients and DREF values were derived independently by D. Grahn using least squares methods and forcing the regression through the observed control incidence intercept.

[b] DREF (Dose Rate Effectiveness Factor) $= \frac{\text{Effect per rad at high-dose rate}}{\text{Effect per rad at low-dose rate}} = \frac{\alpha_L}{\alpha_{Ex}}$

where the effect/rad represents the linear regression coefficients obtained for the high-dose-rate and low-dose-rate data as discussed in Section 9.

[c] Numbers in parenthesis denote dose range for calculation of slopes.

[d] Data used are from Table II of Storer *et al.* (1978).

[e] Based on data from Table IX of Upton *et al.* (1970).

TABLE 9.4—*Protraction factors for available experimental data*

Animal data	α_L	α_{Ex}	PF[a]
Life shortening in Beagles (Andersen and Rosenblatt, 1969; Casarett and Eddy, 1968) (8 rad min^{-1} vs 0.006–0.06 rad min^{-1})	2.68 (0–300)[b]	0.21 (0–1640)[b]	12.8
Life shortening in mice (Grahn and Sacher, 1968; Grahn, 1970) (several strains) (56 rad d^{-1} vs 0.3 rad d^{-1})	Derivation provided in Section 8 (estimates of α_L and α_{Ex} not possible)		10
Life shortening in RFM mice (Upton *et al.*, 1967) (6.7 rad min^{-1} vs 0.0004 rad d^{-1})			
a. Males	0.75[c]	0.075[c]	10
b. Females	0.33[c]	0.05[c]	6.6
Leukemia in LAF female mice (Grahn *et al.*, 1972) (2–20 rad min^{-1} vs 0.01–0.06 rad min^{-1})	Estimated from 37% effectiveness level (derivation of α_L and α_{Ex} not possible)		

[a] PF (Protraction Factor) $= \frac{\text{Effect per rad at high-dose rate}}{\text{Effect per rad at low-dose rate}} = \frac{\alpha_L}{\alpha_{Ex}}$

[b] Numbers in parenthesis denote dose range for calculation of slopes.

[c] Data used are from Table V, Upton *et al.* (1967).

induction in experimental animals may extend from one appearing as a threshold to a nearly-linear nonthreshold dose response. Therefore, it is clear that there can be no single dose-rate effectiveness factor (DREF) to apply to all neoplasms, and each tumor type must be considered individually.

The DREF values for the animal tumor systems for which sufficient data are available are shown in Table 9.3. These values were derived,

except where noted, as described in Section 2 from the ratio α_L/α_{Ex} where α_L is the slope derived from a linear regression for the high-dose-rate data and α_{Ex} is the slope derived for low-dose-rate data. When possible, the experimental values were weighted by the inverse of their calculated variance. It should be pointed out that in some instances (notably life shortening in RFM and BALB/c mice, thymic lymphoma, ovarian tumors, and Harderian gland tumors) a linear model does not provide an adequate description of the high-dose-rate data, particularly in the dose region below 50 rads. Similarly, linear models do not adequately describe the data at low-dose rate for thymic lymphoma or ovarian tumors. In the latter cases, a linear dose-response relationship can be rejected statistically; and quadratic or linear-quadratic equations provide better fits. However, in the interest of estimating the range of DREF values, a single estimate obtained by the α_L/α_{Ex} ratio should be useful, in particular for doses in the 100–200 rad range. It should be recognized that at lower total doses, the DREF values are likely to be smaller and, in theory, are likely to approach 1.0 at very low total doses.

Listed separately in Table 9.4 are the differences in effectiveness observed for life shortening or leukemogenesis under conditions of dose protraction. It is apparent from the table that protraction tends to reduce the effectiveness of the radiation exposure to a greater extent than does reduction of the dose rate.

10. Tumorigenesis in Human Populations

In the following section, human data on radiogenic cancer are examined from the standpoint of possible influences of temporal distribution of dose. Risk coefficients (effect/dose) were developed primarily to allow quantitative comparison among exposures that occurred under different sets of conditions.

10.1 Leukemia

A leukemogenic effect of exposure to low-LET radiation has been investigated in a variety of human populations. The principal studies are summarized in Table 10.1. All but three of the studies (A1, A8, and B4) show risk ratios, observed/expected, significantly greater than unity. The studies represent a variety of types of exposure and of types of populations and taken together are generally accepted as substantial proof of radiogenic leukemogenesis in human beings. Despite the strength of this evidence, the group of studies offers only limited possibilities for describing the variation of leukemia incidence with dose and dose rate.

Three of the reported studies (A2, A5, and A11) include sufficient numbers of cases at a range of *doses* to permit investigations of the nature of the dose-effect relationship. None of the studies includes a sufficient range of *dose rates* to allow an estimate of a dose-rate effect. Dose rates do vary widely, however, from one study to another; and Marinelli (1970) has speculated from the inter-study comparison as to the dose-rate effect.

The three studies that permit internal investigations of the dose-response relationship are studies of the A-bomb survivors (Study A5, Figure 10.1); of patients treated for ankylosing spondylitis with radiation therapy to the spine (Study A2); and of infants exposed prenatally during diagnostic examination of their mothers (Study A11). All three studies involve high-dose rate (in excess of 5 rads per minute). In none of the studies do the data define the shape of the dose-response curve

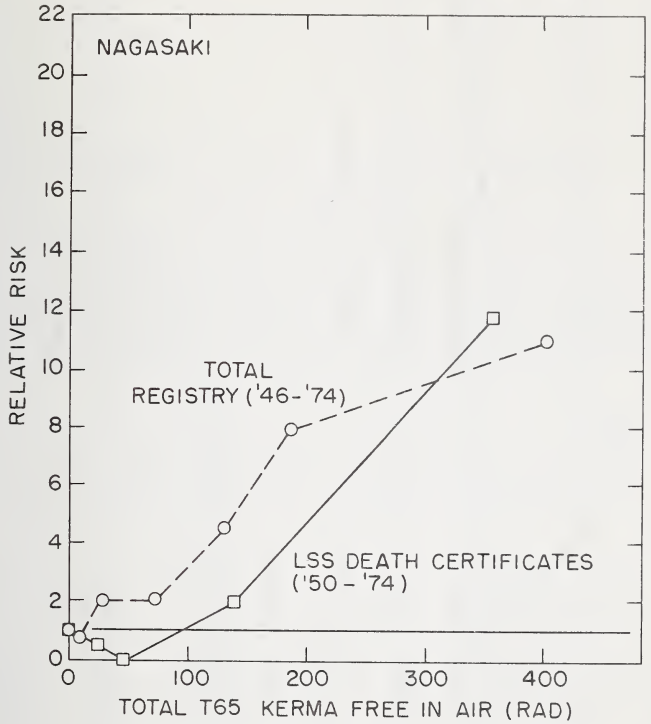

Fig. 10.1. Relative risk vs. total kerma in air, for leukemia in Nagasaki. Data from both the Registry and the Life Span Study are shown (From Beebe *et al.*, 1978).

unequivocally, either to establish an increasing slope with increasing dose, as suggested by the experimental data in animals, or to reject it. Doses in the A-bomb study are in the range of 10 to 600 rads; in the ankylosing spondylitis study, 250 to 2,750 rads; and in the prenatal exposures, probably 1 to 5 rads. In the study of Nagasaki A-bomb survivors, the curve for mortality from all forms of leukemia combined in members of the life-span study (Figure 10.1) has been interpreted by Rossi and Kellerer (1974) to be more consistent with an increasing slope than with a constant slope. The curve for mortality from leukemia in members of the entire Nagasaki registry, however, suggests a decreasing slope and is consistent with a constant slope. The life-span study is more soundly established in a population identified before the diagnosis of leukemia, but is severely limited in number of persons at risk and number of cases. The total registry includes many more exposed people and cases and, therefore, gives narrower confidence limits in analysis of curve shape, but is subject to severe potential bias because of uncertainty of the identification of the population.

TABLE 10.1.—*Summary of data on selected population studies on low-LET radiation and leukemia*[a]

Population	Reference	Number of Subjects Irradiated	Period after Irradiation on which Risks are Based (Years)	Person-years	Estimated External Exposure (R)	Estimated Mean Bone Marrow Absorbed Dose (rad)	Observed / Expected	Relative Increase[e] in Risk Percentage/rad	Absolute Increase[f] in Risk Added cases per 10^6 Person-year-rad
A. High Dose Rate									
1. Malignant Gynecologic Disorders	Hutchison (1968)	23,463	0–15	61,497	882–4,412	50–1,500	4/5.8 = 0.7	—	—
2. Ankylosing Spondylitis	Court Brown and Doll (1965)	14,554	0–25	141,796	250–2,750	372	52/5.48 = 9.5	2.3	0.9
3. Benign Gynecologic Disorders	Alderson and Jackson (1971)	2,068	0–24	28,125	550–1,050	136	6/1.3 = 4.6	2.6	1.2
4. Thymus	Hempelmann *et al.* (1967)	1,451	0–35	26,118	60–600	65	6/0.96 = 6.2	8.0	3.0
5. Atomic Bomb (Nagasaki)	Jablon and Kato (1971)	5,842	6–25	105,501	10–600	63[b]	12/5.3 = 2.3	2.1	1.0
6. Atomic Bomb (Nagasaki children < 10y)	Jablon and Kato (1971)	1,810	6–25		10–600	47[b]	8/0.8 = 10	19.1	4.2[g]
7. Tinea capitis	Albert and Omran (1968) Schultz and Albert (1968)	2,043	0–22	30,645	200–400	30	4/0.9 = 4.4	11.3	3.4
8. Fetus (Atomic Bomb)	Jablon and Kato (1970)	1,292	0–10	12,605	1–500	21[b]	0/0.45 = 0	—	—
9. Diagnostic x ray	Gibson *et al.* (1972)	22[e]	0–20			10	22/6.7 = 3.3	23.0	18
10. Fetus (New England)	MacMahon (1962)	77,000	0–10	616,000	0.5.2	1	47/33.8 = 1.4	40.0	21.4
11. Fetus (U.K.)	Stewart *et al.* (1958)	79[d]	0–10		0.5–2	0.8	79/44.3 = 1.78	97.5	34.1[h]
B. Low Dose Rate									
1. Radiologists (Cohort 1920–49)	Matanoski *et al.* (1975a; 1975b)	2,677	0–50	70,093		600	22/8.1 = 2.7	0.28	0.3
2. ^{32}P. Polycythemia vera	Mayo (1973); Modan and Lilienfeld (1965)	102	0–14	858		300	9/1.5 = 6.0	1.7	29
3. ^{131}I. Carcinoma thyroid	Pochin (1969)	215	0–19	1,046		260	4/0.08 = 50	18.8	14
4. ^{131}I. Thyrotoxicosis	Saenger (1968)	21,690	0–21	145,000		8–16	17/20.9 = 0.8	—	—

[a] Modified from NAS (1972), Modan and Lubin (1974).

[b] Kerma (K) converted to absorbed dose (D) by $D = .56\ K$ rad for adults, $D = .64\ K$ rad for children, $D = .42\ K$ rad for fetuses (Kerr, 1978).

[c] Actual male cases with chronic myeloid leukemia receiving more than 20 trunk diagnostic x-rays (out of a study population of 1,414 male and female cases of leukemia).

[d] Actual cases wiih leukemia receiving abdominal x-rays (out of a study population of 619 cases of leukemia).

[e] Relative increase $= \dfrac{r-1}{D} \times 100$. $r = \dfrac{\text{Observed}}{\text{Expected}}$. D = Estimated bone marrow absorbed dose (rad).

[f] Absolute increase $= \dfrac{\text{Observed} - \text{Expected}}{\text{Person-Years} \times D} \times 10^6$. The "absolute increase" is the slope of the line between the origin (dose = 0, rate = 0) and the point $(\bar{x}, \bar{y})$, where $\bar{x}$ is the mean dose and $\bar{y}$ the mean rate. This value will in general differ from (a) the slope of the best linear regression or (b) the slope of the best linear regression through the origin. The best linear regression passes through $(\bar{x}, \bar{y})$ but not, in general, through (0, 0). The best linear regression through the origin does not, in general, pass through $(\bar{x}, \bar{y})$.

[g] Absolute increase $= \dfrac{\text{Observed} - \text{Expected}}{\text{Number of subjects} \times 20 \times D} \times 10^6$.

[h] Absolute increase = Relative increase in risk $\times\ 35 \times 10^{-6}\ y^{-1}$ ($35 \times 10^{-6}\ y^{-1}$ is the general population leukemia rate).

Note: Sources of Table Values

A. High Dose Rates

1. Population 1. All observed data taken from the reference.
2. Populations 2, 3, 4, 7. All observed data taken from BEIR pages 117, 118 (NAS, 1972).
3. Population 5. All observed data taken from BEIR (NAS, 1972). Marrow dose of 113 from BEIR page 117, corrected according to note *b*. Relative and absolute increase computed by using corrected doses.
4. Population 6. Observed number of subjects, period after irradiation, external exposure, observed/expected taken from reference. Marrow dose of 70 taken from Modan and Lubin (1974), corrected according to note *b*.
5. Population 8. Observed number of subjects, period after irradiation, person-years, exposure, marrow dose of 51, observed number of cases taken from the reference. Marrow dose corrected according to note *b*. Expected number of cases of leukemia computed from expected number of cases of cancer given, 0.75, ratio of leukemia to cancer, 578/947, taken from Segi and Kurihara (1962).
6. Population 9. Observed number of subjects, period after irradiation, observed/expected taken from the reference. Marrow dose of 10 taken from Modan and Lubin (1974). Absolute increase in risk taken from Modan and Lubin (1974).
7. Population 10. Observed number of subjects, period after, person-years, external exposure, marrow dose taken from BEIR page 163 (NAS, 1972). Observed/expected taken from the reference.
8. Population 11. Observed number of subjects, observed/expected taken from the reference. Period after irradiation, external exposure, marrow dose taken from BEIR page 163 (NAS, 1972).

B. Low Dose Rate

1. Population 1. Observed number of subjects, person-years, observed/expected, period after irradiation (0–50 years) taken from reference. Marrow dose of 600 rads taken from Modan and Lubin (1974).
2. Population 2. Observed number of subjects, period after irradiation, person-years, observed/expected taken from Modan and Lilienfeld (1965). Marrow dose of 300 rads taken from Mays (1973).
3. Populations 3, 4. All observed data taken from the references.

Data of the ankylosing spondylitis study (Court Brown and Doll, 1957; 1965) suggest an increasing slope with increasing dose, although the departure from linearity is largely due to a single dose-incidence point at high dose; and a constant slope cannot be rejected. Linear and quadratic regression curves for the ankylosing spondylitis study are, respectively

$$y_1 = .79 \times 10^{-6} D, \text{ and} \tag{10.1}$$

$$y_2 = -.034 \times 10^{-6} D + .57 \times 10^{-9} D^2. \tag{10.2}$$

Since the linear coefficient of the quadratic curve is negative, the two coefficients cannot be interpreted in terms of relative effects of single and complex radiobiologic events. Clearly, however, if both y_1 and y_2 give good fits to the observed data, fits may also be obtained with linear and quadratic coefficients bearing relationships similar to those found in experimental exposures of laboratory animals. For example, with a ratio of 100 (linear coefficient/quadratic coefficient = α/β = 100 rads),

$$y_3 = .051 \times 10^{-6} D + .51 \times 10^{-9} D^2. \tag{10.3}$$

Data of the prenatal exposure experience are interpreted by Stewart and Kneale (1970) as implying a linear increase in leukemia incidence with number of diagnostic x-ray studies. The dose information in this study is too insecure to support more extensive analysis. As will be noted below, there is further question as to whether the increased incidence of leukemia in the several studies of prenatal irradiation may reflect the effect of unidentified confounding factors rather than a radiogenic effect.

One may attempt to evaluate the nature of the dose-response relationship at high-dose rate by inter-study comparison among the 11 high-dose-rate studies in Table 10.1. If all studies were otherwise comparable, a linear dose-response relationship would be reflected in uniform absolute risks per rad among the studies; while an increasing slope of the dose-response curve would result in increasing absolute risk per rad with increasing dose. Unfortunately, the several studies are known not to be comparable with respect to a number of variables whose effects may reasonably be suspected to be significant. The most important of these is age, mentioned below, and others of probable importance are length of follow-up, fractionation, and sex of subjects. If these uncontrolled associations are ignored, the group of 11 studies appears to suggest strongly a falling absolute risk per rad with increasing dose, contrary to the relation postulated. Thus, the three groups with the lowest doses (A9, A10, and A11) have the highest absolute risks per rad; and the two highest dose groups (A1 and A2) have among

the lowest absolute risks per rad. The high risk reported in Study A9 is the risk in males only, and no excess risk was seen in females. There was no prior hypothesis of a sex differential in sensitivity to diagnostic level radiation. While the high risk for males need not be questioned, this rate cannot be accepted as comparable with tabulated values from other studies which represent the risks for the total populations included. Studies A10 and A11 involve fetal exposure and may represent a biologic difference from the studies of post-natal exposure. Further uncertainties of the fetal studies are discussed below.

A possible explanation for low slopes (absolute risks per rad) in the high-dose studies might be that the observations were in a very high dose range beyond the dose of maximum effect. This would seem to be the case in Study A1, involving the high doses used in radiotherapy of malignant disease. In Study A2, this explanation would be supported by the finding of a downturn in the dose-response curve within this study. No such downturn is seen, and the observed incidences at the highest doses deviate from the linear regression in the direction of being higher than predicted. The quadratic curve gives a particularly good fit in the highest observed doses (above 2,000 rads) with some observed incidences higher than predicted and some lower in this range. A suggested explanation for the failure to see a downturn at the high doses in this study is the fractionation of dose in these radiation treatments. The other two studies, A5 and A11, which permit within-study observations of the dose-response curve are limited to doses below 600 rads and, as expected, do not show a fall in incidence at the highest doses within either study. These comparisons are simply without meaning in view of the heterogeneity of the studies and of the sampling variability of the risk estimates for most of the studies (A1, A3, A4, A6, A7, and A8 each involve fewer than 10 leukemias observed in exposed persons). The most striking potentially confounding variable is age of exposed populations, with the highest estimates of risk per rad in the youngest ages (fetal exposure) and the lowest estimates in the patients with typically adult diseases, ankylosing spondylitis and cervical cancer.

A similar lack of interpretable evidence results from interstudy comparison of the 4 low-dose-rate studies. The wide uncertainty of the exposure dose in Study B1, radiologists exposed occupationally, has been discussed in Section 3.5.4 above in connection with life span effects. In Table 10.1 we have used the estimate 600 rads as the mean cumulative lifetime marrow dose. In view, however, of the relatively high incidence of aplastic anemia reported on the death certificates of this group, it seems likely that the dose may have been appreciably larger than 600 rads. Study B3, of ^{131}I therapy for thyroid cancer,

suffers from inadequate sample size (4 observed, 0.08 expected). The studies of patients with thyrotoxicosis (Study B4) and polycythemia vera (Study B2) involve diseases with possibly carcinogenic drug therapy and with biologic relationship with leukemia quite apart from the radiotherapy of the diseases. As with the high-dose-rate studies, no interpretable association of dose with risk is found in this inter-study comparison.

It has been noted that none of the studies in Table 10.1 includes a sufficient range of dose rates to allow an estimate of a dose-rate effect. As with the consideration of the dose effect, one may attempt to consider the dose-rate effect by comparing studies with one another. The 11 high-dose-rate studies have overall slopes (absolute risk per rad) ranging from 0 to 34.1 added cases per million person-year-rad. The 4 low-dose-rate studies have slopes of 0, 0.3, 14, and 29. As with the evaluation of dose effect, we believe that inter-study comparison cannot be interpreted relative to a possible dose-rate effect.

Study A11 of prenatal irradiation (Stewart *et al.*, 1958) includes the largest number of leukemias among exposed individuals (79 cases) of all of the tabulated studies. Precise doses to these fetuses are not known, but the investigators have demonstrated an increasing leukemia incidence associated with increased number of x-ray films to the mother in the relevant pregnancy. Table 10.1 indicates a relative risk of 1.78, one of the smallest relative risks tabulated, but, because of the presumed low doses of a few rads, the absolute increased risk per rad is estimated to be 34.1 cases per million person-year-rad, the largest absolute risk shown. If this estimate can be accepted as valid, it implies that low-dose exposure to the fetus results in the greatest absolute risk per rad of all human radiation exposures studied. MacMahon and Hutchison (1964) reviewed all reported studies (10 studies) of leukemia risk following prenatal exposure as of 1964 and showed that when sample sizes were considered, all of these studies gave results consistent with those of Stewart *et al.* (1958). The investigators in this group of studies considered a number of potential confounding factors and found the estimate of the radiation factor was decreased but not eliminated after control for all factors for which control was possible.

More recently, Mole (1975a) investigated the variable of multiple births (twinning) and found the radiation effect present in both single and twin births. These attempts to control confounding variables were done in order to determine whether the associations found can reasonably be interpreted as implying a cause-effect relationship. An extensive discussion of the problem of making such a causal interpretation from observational data is given in the Surgeon General's Report on Smoking and Health (Smoking and Health, 1964). In that discussion,

the strength of the relationship is identified as one of the important characteristics lending support to a causal interpretation. The strength in Study A11 may be measured by the risk ratio of 1.78. While no limiting value of risk ratio can be stated that must be shown to permit a causal interpretation, it may be questioned whether analytic control of confounding factors can ever be sufficient with a risk ratio as low as 1.78. If a very large risk ratio, for example a 10-fold increase in risk, is observed, it is difficult to support an argument that some unsuspected confounding factor may cause so strong an association. A 2-fold increase, however, may more easily be explained as such an artifact; and a ratio less than 2 is exceedingly difficult to characterize as causal. A solution to this problem is often found in intervention studies, such as clinical trials or prophylactic trials. No such trials of *in utero* radiation have been done, but two studies may be cited as simulated trials in that radiation exposure was given to persons not selected on the basis of individual medical indications.

Study A8, Table 10.1, shows no leukemia following the much higher radiation doses to fetuses as a result of the atomic bomb exposures in 1945. This result at high dose is inconsistent with the linear nonthreshold extension of the effect above at low dose. Oppenheim *et al.* (1974) have reported on a simulated, or "natural," experiment, in which all pregnant women in one hospital during one year underwent x-ray pelvimetry as a result of an administrative decision. These investigators found no radiogenic leukemia, although the number of exposed fetuses was too small to exclude the possibility of a risk of the magnitude reported in the earlier fetal x-ray studies. The question of a leukemogenic effect of *in utero* radiation remains unsettled. If the estimates shown in Studies A10 and A11, Table 10.1, are valid estimates of the effect at low doses and are compared with available estimates of effects at high doses in other, non-fetal populations, they contradict the hypothesis of increasing risk per rad with increasing dose. Because of both the questionable validity of these estimates and the questionable comparability of fetal with non-fetal exposure, these findings must be considered uninterpretable relative to any possible effects of dose or dose rate on the risk per rad of leukemia.

10.2 Breast Cancer

Epidemiologic evidence for a radiation-induced excess of breast cancer in irradiated women is available primarily from studies of 1) women subjected to multiple fluoroscopic examinations of the chest in the treatment of pulmonary tuberculosis with artificial pneumothorax; 2) women given x-ray therapy to the breast for postpartum mastitis;

and 3) women surviving atomic-bomb irradiation at Hiroshima and Nagasaki. The evidence from these three sources, evaluated independently by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1972) and by the National Academy of Sciences-National Research Council Committee on the Biological Effects of Ionizing Radiation (BEIR) (NAS, 1972), was interpreted to indicate carcinogenic effects on the female breast. Evaluation of the magnitude of the carcinogenic risks per unit dose, however, was complicated by the small size of some of the samples available for analysis and by uncertainty as to the contribution of risk factors other than radiation. In spite of these uncertainties, the BEIR Committee tentatively concluded that the excess incidence of cancer in the three populations, averaged over all radiation doses and all ages, amounted to roughly 2–8 cases per million person-year-rad between the tenth year after irradiation and the end of the follow-up period, some 15–20 years later.

During the interim since the UNSCEAR and BEIR evaluations, additional observations have amplified and reinforced the earlier findings as shown in Table 10.2.

In *women subjected to multiple fluoroscopic examinations* in the pneumothorax treatment of tuberculosis, the data have been extended by: 1) observation of additional cancer cases and cancer deaths in the original series of Nova Scotia patients; and 2) corroboration of the findings in the Nova Scotia series by similar observations on other series of multiple fluoroscoped patients in Ontario and in Massachusetts. The findings in the Nova Scotia series (Myrden and Quinlan,

TABLE 10.2.—*Breast cancer after exposure to ionizing radiation*[a]

Study Population	Type of radiation	Duration of radiation exposure	Duration of Follow-up (years)		Period after Irradiation on which risk estimates are based (years)	Number of Subjects	Person-years
			Range	Mean			
A-Bomb Hiroshima + Nagasaki, 1945, (Jablon and Kato, 1971)	$\gamma + n$	< 10s	25	25	5–24	12,400	235,345
Fluoroscopy, 1940–49, (MacKenzie, 1965)	x	weeks to years	15–32	21	11–28	308	2,885
Fluoroscopy, 1930–54, (Boice and Monson, 1977)	x	weeks to years	15–44	25.6	10–44	1,047	18,511
Mastitis, (Shore *et al.*, 1977)	x	min to weeks	10–34	25.2	10–34	571	9,500

[a] Point estimate: $\frac{\text{Observed} - \text{Expected}}{\text{Person-Years} \times \text{Mean Dose}}$

1974; Myrden, personal communication, 1975) have revealed an additional 14 breast cancers, bringing to 36 the total number of breast cancers in some 308 fluoroscoped women followed for up to 32 years after initial exposure (6417 person-years), as compared with 8 cancers in 493 non-fluoroscoped women followed for a comparable period (roughly 8219 person-years). The average age of the women at the time of fluoroscopy was about 26 years, and the average age at which their cancers were diagnosed was about 44 years. None of the tumors was observed during the first 10 years of follow-up, and 10 of the 14 deaths from breast cancer occurred during the last eight years of follow-up. Most of the women had been fluoroscoped "unilaterally," and in such women 20 of the 27 tumors that were observed occurred on the "irradiated" side.

The excess of breast cancer increases in proportion to the total number of fluoroscopic examinations. Estimation of the dose-incidence relationship, however, is complicated by uncertainty about the doses actually received by both breasts. On the assumption that the average dose to the breast per fluoroscopy was 7.5 rads, the mean cumulative dose has been calculated to be about 1200 rads (NAS, 1972). Based on this dose estimate and the assumption of a linear non-threshold dose-incidence relation, the cumulative risk during the 11th to the 28th year of the follow-up corresponds to approximately 8.4 cases of breast cancer (or 3.8 cancer deaths) per 10^6 person-year-rad to both breasts. Although the BEIR Committee arrived at its dose estimate by assuming an average skin exposure of 10 R per fluoroscopy, which it adjusted to a value of 7.5 rads for underlying breast tissue at a depth of 1 cm, the value at a greater depth would have more nearly approximated

Mean dose (rad)	Mean age at irradiation (y)	Nature of Control	Relative risk, Observed/Expected	RBE	Percent increase in relative risk per rad	Excess Cases per 10^6 person-year-rad	Excess Cases per 10^6 person-year-rad 90% Limit	
						Point[a] Estimate	Lower	Upper
80.6	26.8	0–9 rad	$\frac{82}{48.2}$ =1.7	1 + 5	0.87	2.4	1.6	3.2
1,215	26	Patients not fluoroscoped	$\frac{36}{6.2}$ =5.8	1	0.40	8.4	5.5	11.5
150	25	Patients not fluoroscoped	$\frac{38}{20.9}$ =1.8	1	0.53	6.2	2.8	10.7
247	27.5	3 non-irradiated groups	$\frac{37}{16.88}$ =2.2	1	0.47	8.3	3.1	16.0

the mean dose to the breast. At a depth of 2.5 cm, for example, the corresponding dose value is about 3.6 rads. If the latter value is substituted for 7.5 rads, the estimated risk per rad is essentially doubled. In the face of uncertainty about the actual distribution of doses to the tissues of both breasts, however, further refinements in the risk estimates for this sample would not seem warranted at this time.

The observations in fluoroscoped women of Nova Scotia have been confirmed by comparable findings in a small series of women subjected to multiple chest fluoroscopies in Ontario (Cook *et al.*, 1974). Similarly, in a series of 1047 women fluoroscoped in two Massachusetts tuberculosis sanitoria (Boice and Monson, 1977), the incidence of breast cancer has been observed to be higher (41 cases observed versus 23.3 expected on the basis of rates from the Connecticut tumor registry) than in a comparison group of 717 nonfluoroscoped women (15 cases observed versus 14.1 expected). In the irradiated women, the incidence increased with the number of fluoroscopies up to a total of 150 fluoroscopies, above which it appeared to decline. When plotted as a function of the estimated mean dose to breast tissue, however, the dose-incidence curve did not deviate significantly from linearity (Boice *et al.*, 1978). No excess of tumors was evident until more than 15 years after the onset of irradiation; and from years 10–44 after irradiation, the overall excess risk was estimated at 6.2 cases per 10^6 person-year-rad.

The follow-up of *women treated with x rays for postpartum mastitis* in upstate New York (Mettler *et al.*, 1969) has been extended in a recent resurvey, some seven years subsequent to the preceding study. The following three groups of non-irradiated controls were included in an effort to ascertain any possible complicating influence of mastitis or other host factors: 1) 554 non-irradiated sisters of the treated women; 2) 539 women with postpartum mastitis at a hospital in New York City who were not treated with x rays; and 3) 206 sisters of the latter women, who had no history of acute mastitis (Shore *et al.*, 1977). This recent survey extended the follow-up of the original sample of women treated with x rays and analyzed the distribution of tumors in relation to dose, dose fractionation, time after irradiation, age at exposure, and other variables. In the 571 irradiated women, whose duration of follow-up averaged 25.2 years (14,428 total cumulative person-years (PY) at risk), 37 cases of breast cancer were observed, to give an age-adjusted rate of 2.8 per 10^3 PY, as compared with 1.4 per 10^3 PY in the controls (34 cases per 25,342 PY, with an average follow-up of 25.6 years). The incidence of benign breast tumors was similarly elevated in the irradiated women (2.1 per 1000 PY versus 1.1 per 1000

PY). The tumor rates among the various control groups did not differ significantly. In the irradiated women, no excess of tumors was apparent during the first decade after exposure, which suggests a minimal latent period of about 10 years. The cumulative incidence of tumors, both benign and malignant, increased with dose from the lowest dose (40 rads average dose to both breasts) up to 300–400 rads, above which the incidence turned down. The dose-incidence curve was compatible with a linear (nonthreshold) function throughout the dose range 0–400 rads, above which the incidence turned down. The total cumulative cancer excess for the period 10–34 years after irradiation corresponded to a relative risk of 2.2, an increase of 0.47 percent per rad, a doubling dose of 215 rad, and an absolute risk of 8.3 cases per 10^6 person-year-rad. The excess was insignificantly higher in women who received their irradiation in 3–4 fractional exposures than in those who received a comparable total dose in 1–2 exposures.

In *women who survived atomic-bomb irradiation* and for whom dose estimates are available, a total of 187 cases of breast cancer have been identified during the period 1950–1969 (McGregor *et al.*, 1977). The incidence increased with dose, corresponding to about 2.4 cases per 10^6 person-year-rad to breast tissue[9] over the 19-year period for women aged 10 or older at the time of irradiation. The dose-incidence curves for Hiroshima and Nagasaki appear similar, suggesting that neutron and gamma radiations were not greatly different in their carcinogenic effects on the breast; and both curves are consistent with a linear (nonthreshold) dose-incidence relationship over the dose range from 0 to 200 rads. No better fit to the A-bomb data was obtained when a dose-squared term was introduced, either for total dose or for the component of dose due to gamma radiation alone. For both cities, Hiroshima and Nagasaki, the observed age-standardized incidence for the dose interval 100–199 rads is greater than the linear estimate, while the incidence for the interval 200+ is less than estimated, values consistent with a sigmoid dose-response relation. This study also permits investigation of a possible carcinogenic effect of doses in the dose range below 100 rads. When the dose groups characterized by means of 0, 2.9, 16.7, and 54.3 rads are examined for a linear trend of increasing incidence with dose, the null hypothesis of no trend is rejected at probability level .06 (Land and McGregor, 1979). That is, the trend of actual observations at low-dose levels themselves almost reaches a conventional significance level.

[9] Kerma-in-air (K) at a location corresponding to the center of the body converted to absorbed dose (D) (in rads), as a first approximation, by $D/K = 0.80$, for gamma and neutron radiation.

The three types of exposure, fluoroscopy, therapeutic irradiation, and atomic-bomb irradiation, all produce a significant increase in incidence of female breast cancer. All three types of exposure are reported in sufficient detail to permit estimates of incidence over a range of doses, with doses as low as 100 and as high as 400 rads in all cases. The atomic-bomb experience permits estimates at additional lower doses and the fluoroscopy series permits estimates at additional much higher doses. All of the studies indicate significant increases in incidence with dose. The numbers of cases of breast cancer, however, are limited; and none of the series allows detection of small departures of this increase in incidence from linearity. The least-square regression of incidence on a second order power function of dose results in a dose-squared coefficient (β) not significantly different from zero for all series (Table 10.3). For the Massachusetts fluoroscopy study (Boice *et al.*, 1979), the linear (α) and dose-squared (β) coefficients are both positive; while for the other two series, therapeutic irradiation and atomic-bomb irradiation, α is positive and β is negative. The three series suggest that linear interpolation from doses in the range of 200 to 400 rads to the range of 0 to 10 rads would result in an incidence estimate that was either negligibly too high (fluoroscopy) or was negligibly too low (therapeutic or atomic-bomb irradiation). The instability of the coefficients is such that an α/β ratio of 100 rads is consistent with the fluoroscopy series, but is outside the conventional confidence limits of the other two series.

None of the three types of exposure involves sufficient range of factors other than dose to permit an estimate of the effect of these other factors. Intercomparison of studies, however, may be investigated for evidence of an effect of dose rate or of x-ray beam energy or both. Such a comparison must be interpreted with caution, since the populations exposed and the methods of investigation differ in many ways

TABLE 10.3—*Regression coefficients—Regression of incidence of breast cancer on dose.*

	Linear[a]		Second Order Power Function[b]		
	I_0 Cases per 10^5 person-year	α Cases per 10^6 person-year-rad	I_0 Cases per 10^5 person-year	α Cases per 10^6 person-year-rad	β Cases per 10^7 person-year-rad^2
A-Bomb Hiroshima + Nagasaki 1945	22 ± 2	2.2 ± 0.5	21 ± 2	3.6 ± 1.3	−0.61 ± .053
Fluoroscopy 1930–54	100 ± 20	5.1 ± 1.4	110 ± 20	3.4 ± 3.7	.047 ± 0.93
Mastitis	160 ± 20	5.6 ± 1.4	150 ± 20	9.0 ± 3.7	−.083 ± .084

[a] Linear. $I_D = I_0 + \alpha D$.

[b] Second Order. $I_D = I_0 + \alpha D + \beta D^2$.

and other factors may produce apparent associations between dose rate or beam energy and cancer incidence. Such secondary associations may also obscure true associations. The fluoroscopy 1930–1954 study and the study of radiotherapy for mastitis have been investigated for such a comparison. Relevant physical factors of these studies are summarized in Table 10.4.

The two series overlap extensively in total dose and differ by a factor of less than 7 in dose rate, expressed as rad s^{-1} during exposure fractions. Dose rates in both cases are in the range generally described as "high," and no differential effect on cancer incidence would be expected as a result of this factor. The beam energy levels differ by a factor of about 3, and this difference is known from laboratory experimental studies to result in a difference in incidence of a variety of biologic endpoints of 2-fold or more, in the direction of greater incidence with lower energy level.

The remaining three physical measures, dose per fraction, duration of fraction, and number of fractions, may be thought of as indices of degree of fractionation. A high degree of fractionation, however, with limited total dose and prolonged total time from first to last fraction must be considered as biologically equivalent to low-dose rate, even when the dose rate itself is in fact in the high range. Thus, the highly fractionated exposure in the fluoroscopy series involves the high-dose rate of about 0.7 rad s^{-1}, but the duration of exposures is so short that doses per fraction are in the low range of 0.2 to 20 rads. This exposure pattern would be expected to be biologically equivalent to low dose-rate exposure. Laboratory experimental studies show a reduced biologic effect per unit dose with either high degree of fractionation or a low-dose rate (Bond *et al.*, 1978; Bond, 1978).

From the above relationships it can be predicted that the mastitis and fluoroscopy studies would be affected by both the different energies of the radiations and the different degrees of fractionation. The expected direction of the effects would be to produce greater cancer incidence in the fluoroscopy study because of the lower energy x rays and a greater incidence in the mastitis study because of the lesser

TABLE 10.4—*Physical factors for the mastitis and fluoroscopy series.*

	Mastitis	Fluoroscopy 1930–54
Total dose (rad)	100–1,100	1–1,027
Dose rate (rad s^{-1})	2.5	0.4–.9
Energy (kVp)	175–270	70–85
Dose per fraction (rads)	100–200	0.2–20
Mean duration of fraction(s)	40–80	3–60
Number of fractions	1–11	1–700

degree of fractionation. The actual observation of a greater incidence, although not significantly greater, in the mastitis series is consistent with a substantial fractionation effect more than off-setting any effect of radiation energy that may be present. If the radiation energy in this human experience has an effect as great as 2-fold, as seen in laboratory studies, then the fractionation effect, in the opposite direction, must be somewhat greater than 2-fold. Insofar as fractionation as described in the fluoroscopy series is biologically equivalent to low-dose rate, these findings may be considered a possible demonstration in human radiation carcinogenesis of a low-dose-rate effect. It is emphasized, however, that other explanations of the observed cancer rates remain acceptable. For example, substantial errors in estimation of exposure, particularly in the fluoroscopy series, are possible. Other variables differentiating the two studies may alter the apparent dose-response relationship. And there may be no energy-level effect in the human breast tumor response, and consequently no reason to involve the explanation of an overriding fractionation effect to counteract the energy-level effect. If the energy-level effect is ignored and if the lower estimate of mean dose to breast is used in the Nova Scotia fluoroscopy series, the low-dose-rate (fluoroscopy) exposure is found to be associated with an incidence more than twice that of the high-dose-rate (mastitis) exposure. This explanation contradicts the hypothesis of a positive association of dose rate in the leukemia incidence. We do not believe these two assumptions can be supported, since the absence of an energy-level effect contradicts experimental evidence and the dose estimate in this fluoroscopy series is highly uncertain.

10.3 Thyroid Cancer

An excess incidence of thyroid neoplasms, amounting to an estimated 1.6–9.3 cases of thyroid cancer per million children-year-rem, has been observed in several series of patients subjected to x-ray therapy of the neck region in infancy, as well as in children among atomic bomb survivors and Marshall Islanders exposed to fallout (NAS, 1972, p.120; UNSCEAR, 1972, p.429). Although the data are not adequate to define the shape of the dose-incidence curve, it is noteworthy that an excess incidence of magnitude approximately equal to that predicted from the above studies by a linear model has been observed in one of two series of children given therapeutic x irradiation to the scalp for the treatment of ringworm (Modan *et al.*, 1974). The average dose to the thyroid gland has been estimated to be 6 to 7 rads (Table 10.5). The suggestion that the risk per rad at this dose level

TABLE 10.5—*Estimated risk of thyroid neoplasms after childhood irradiation: selected studies*

Time of exposure	Radiation exposure		Number exposed	Type of controls	Follow-up years: No. and (mean)	Benign tumors		Malignant tumors		Reference
	Type of radiation	Mean thyroid dose (rad)				Obs/Exp[a]	Risk/10^6 child rad y	Obs/Exp[a]	Risk/10^6 child rad y	
1926–1957	X-ray therapy	119	2,872	siblings	14–45 (25)	52/3.42	5.9	24/0.29	2.5	Hempelmann *et al.* (1975)
1930–1946	X-ray therapy	399	261	siblings	25–43 (33)	20/0	6.2	13/0.04	4.0	Hempelmann *et al.* (1975)
1932–1954	X-ray therapy	20	958	population rates	14–36 (29)	7/1.3	10.3	1/0.13	1.6	Hempelmann *et al.* (1967)
1949–1960	X-ray therapy	6.5	10,902	siblings, matched pop.	12–23 (17)	N.R.[b]	—	12/1	8.3	Modan *et al.* (1974)
1940–1958	X-ray	6	2,213	clinical controls	11–32 (21)	6/0	21.5	0/0	—	Shore *et al.* (1976); Harley *et al.* (1976)
1945	A-bomb	143	811	unexposed, low dose	25	N.R.[b]	—	6/1.6	1.5	Jablon *et al.* (1971)
1954	fallout	1,010	19	unexposed	20	14/0.19	41.9	1/0.006	2.6	Conard *et al.* (1970, 1975)
1953	fallout	50–120	1,378	unexposed	15	18/13	2.0–4.8	0/0	—	Mays (1973); Hoffman (1976)

[a] Numbers of cases observed/numbers of cases expected.

[b] Benign neoplasms not reported.

could be similar to that at 200–300 rads would argue against the existence of any appreciable curvilinearity in the dose-incidence curve over the dose range in question. However, the dosimetry was evaluated decades after the exposure. The radiation was directed at the scalp with no thought of thyroid exposure. Hence, there is the possibility that doses several times higher than 6–7 rads were responsible for the tumors in question as a result of movement by some children during irradiation so that their thyroids were in the direct x-ray beam, or that other complications could have caused the thyroid region to be included inadvertently in the treatment field. Also, in the exposure geometry of Modan's series, the children's pituitaries were consistently irradiated, a factor which may conceivably have contributed to the induction of the thyroid neoplasms (see Hempelmann *et al.*, 1967; 1975) as specifically pointed out by Modan and Lubin (1974) who stated, "The increased rate of thyroid carcinoma in our cases, though in line with previous observations on radiation induction of this tumor, is puzzling in view of the fact that the dose absorbed by the thyroid was only 6.5 rad. There are some alternative explanations: carelessness during irradiation, an extreme sensitivity of the thyroid gland to irradiation, or tumour production through an hypophyseal/thyroid axis after a high radiation absorbed by the hypophysis...".

In a reconstruction of the doses that may have been received by a group of New York children given similar x-ray therapy to the scalp for the treatment of *tinea capitis*, Harley *et al.* (1976) estimated that the doses were 6 ± 2 rad to the thyroid and 49 ± 6 rad to the hypophysis (pituitary gland). Thus, the pituitary dose appears to be about 8 times higher than the thyroid dose for the *tinea capitis* patients. To date, moreover, no malignant tumors have been observed in the similar series under follow-up by Shore *et al.* (1976) (Table 10.5). It remains to be determined, therefore, whether the risks per unit absorbed dose at the lower dose level (6–7 rads) are actually as large as those at higher dose levels.

A suggestion that low-dose-rate irradiation from ^{131}I is less tumorigenic than irradiation at higher dose rates from x rays, gamma rays, or shorter-lived radionuclides of iodine may be inferred from the follow-up study of children exposed to ^{131}I in fallout in St. George, Utah, depending on the estimated dose to the thyroid (Tamplin and Fisher, 1966; Mays, 1973; Hoffman, D., Personal communication, 1976). The dose to the thyroid was primarily from ^{131}I ingested in cows' milk, as compared with the dose in children exposed to fallout in the Marshall Islands, which was received primarily from shorter-lived radionuclides of iodine ingested directly as well as from external gamma rays (Mays, 1973). In 15 of the 19 Marshallese children on Rongelap Island who were 0–10 years of age at irradiation, thyroid nodules were observed

within 15 years after exposure. The total dose to the thyroid was in the range 700–1400 rads, with a best estimate of 1010 rads (Table 10.5). In the St. George children, whose thyroid dose has been estimated to range from 30 to 240 rads (Tamplin and Fisher, 1966), benign thyroid nodules were detected in 18 of 1378 children within 15 years after irradiation. However, since 13 ± 5 nodules were expected naturally in this population, based on a similar follow-up of non-irradiated children in Safford, Arizona, it can be inferred that 0–10 thyroid nodules may have been induced, with perhaps 5 as a tentative best estimate (Table 10.5). This excess in the St. George population was thus calculated to range roughly from 2.0 to 4.8 nodules per 10^6 person-rad-years, depending on whether the average dose to the thyroid is taken to be 120 rads, as estimated several years ago (see Tamplin and Fisher, 1966; Mays, 1973), or 50 rads, as estimated more recently (Hoffman, D., Personal communication, 1976). Clearly, the data do not suffice to establish a dose rate effect, owing to the large uncertainty in the estimates of the dose to the thyroid.

10.4 Other Cancers

Aside from leukemia, cancer of the thyroid, and cancer of the breast, no data are available for low-LET radiation to indicate the influence of dose and dose rate or the dose-response relationship for cancers of specific types and sites.

10.5 Overall Cancer Mortality

The most recent analysis of mortality rates in U.S. physician specialists (Matanoski *et al.*, 1975a) supports the interpretation that occupational exposure may have caused an excess of the order of 2.5 cancer deaths per 10^6 person-years-rad in pioneer radiologists (Table 10.6), although such a conclusion must be qualified because of uncertainties about the relevant radiation doses to the population in question, as indicated in the sections on life-shortening (Section 8.3) and leukemia (Section 10.1). Whatever its limitations may be, the estimate is not markedly different from the excess per unit absorbed dose in overall cancer mortality observed in A-bomb survivors and x-irradiated spondylitics (Table 10.6). The data for mortality from cancers of all types thus resemble the data for leukemia in failing to disclose marked differences between the radiologists, who received their irradiation at occupational dose rates, and populations exposed at higher dose rates.

TABLE 10.6—*Risk estimates for overall mortality from all types of radiation-induced cancers*

Population group	Age at irradiation (years)	Mean dose to whole body (rad)	Dose rate (rad min^{-1})	Type of radiation	Follow-up (years)	Excess cancer deaths	
						Per 10^6 person-y	Per 10^6 person-y/rad
A-Bomb survivors, Nagasaki	10 +	62[a, b]	100 +	γ	6th–27th	115[c]	1.9
Spondylitics	15 +	375[a]	50 + (Fract)	X	5th–27th	900[d]	2.4
Radiologists	20 +	500–1500[a]	10 + (Fract)	X and γ	44	1500[e]	1–3

[a] NAS (1972).
[b] Assuming dose/kerma = 0.55 (Jones, 1977).
[c] Moriyama and Kato (1973).
[d] Court Brown and Doll (1965).
[e] Matanoski *et al.* (1975a; 1975b).

10.6 Summary of Human Evidence

Quantitative information about the effects of dose rate on carcinogenesis in human populations is fragmentary.

The incidence of leukemia, but not of other types of cancer, in pioneer United States radiologists appears lower, perhaps by a factor of 3 to 4, than that expected for a comparable dose to the whole body, based on the incidence per rad in A-bomb survivors of Nagasaki and other comparable acutely irradiated adult populations. This conclusion suggests that protracted irradiation at low-dose rates from occupational exposure may have been less leukemogenic than exposure at high-dose rates. This interpretation is confounded, however, by uncertainties in the dose estimates and other possible sources of error. Further evidence of a dose-rate dependency for carcinogenesis by low-LET radiation is suggested by the lower incidence per unit dose of thyroid tumors, benign and malignant, in children exposed to ^{131}I in fallout at St. George, Utah, than in other groups of children whose thyroids were irradiated at higher dose rates. Because of uncertainties in the dose estimates, however, and because of the limited numbers of observations to date, the comparison can be considered suggestive at best. The highly fractionated irradiation received by Massachusetts women who were subjected to multiple fluoroscopic examinations of the chest in the treatment of tuberculosis is associated with an excess incidence of breast cancer that is smaller, but not significantly smaller per unit dose, than that in women therapeutically irradiated in only one or a few exposures at high-dose rates. The true effect of the fractionation here may be obscured by the low energy of the x rays used in fluoroscopy. The increase in overall cancer mortality in pioneer United States radiologists is not clearly smaller per unit absorbed dose than that in A-bomb survivors and x-irradiated spondylitics, who were exposed at higher dose rates. This comparison is inconclusive because of uncertainties about the doses received by the radiologists, as well as other limitations in the data.

In a number of studies of irradiated human populations, the rate of increase of risk per unit increase of dose was estimated by the ratio of the incidence in the total exposed population to the mean dose to the tissue of interest for the same population. Although this simplified approach may be dictated by small population size or by limited information as to dose distribution for the population, this sort of information cannot serve to elucidate questions as to the shape of dose-incidence curves or as to the variation of these curves with dose rate. Until sufficiently detailed data become available, estimates made must be presented with clear stipulations as to their uncertainty.

11. General Discussion

In this section a series of considerations which are relevant to quantitative dose and dose-rate relationships in man and lower systems and, therefore, to the applicability of a DREF in man is discussed. Data in the specific sections of the report are discussed first, followed by more general considerations.

11.1 Report Content by Section

Hereditable effects obviously are of considerable importance, not only in their own right, but because the correlation between mutagenic and carcinogenic activity is high and because the mechanisms involved are considered to be similar and related. It has been necessary to rely largely on specific-locus mutation data on mice for quantitative estimates of genetic effects in man because of the paucity of relevant data in the human being (despite studies on human populations exposed over a large dose range). Thus, for over two decades animal data have been used extensively to estimate the absolute risk coefficients for genetic effects in man and it has been recognized explicitly that lowering the dose rate reduces the effectiveness per rad of the radiation. Also, these studies appear to demonstrate that repair of subeffective damage from ionizing radiations can and does occur at the molecular level.

Among the earliest biological endpoints to be studied in a highly quantitative manner were chromosome aberrations. Clearly different dose-response curves were obtained for different dose rates, and it was apparent early that the "$\alpha D + \beta D^2$" formulation fitted the data quite well. The dose-response curves for pink mutations in *Tradescantia* exposed to low-LET radiation have been documented in detail, and these highly quantitative studies encompass a dose range of almost four orders of magnitude (approximately 0.1 rad to 1,000 rads). It has likewise been established, on the basis of extensive direct data, that the curve in the low dose region (the "αD" component) is essentially linear with no apparent threshold. The data also suggest that the dose squared or "βD^2" component of the total effect seen at higher doses is highly dependent on dose rate and may be eliminated completely by

using low doses and/or dose rates. The "αD" component of the effect appears to be independent of dose and dose rate.

Moreover, the studies with *Tradescantia* suggest a difference in the alpha terms observed for relatively low- vs. high-energy x or gamma radiations. Thus, although the dose-response curves for ortho- and lower-voltage x rays and (higher energy) gamma radiations may be very similar in the high dose and dose rate ("βD^2") portion of the curves, the low dose and/or dose rate ("αD") portion of the curves may differ by a factor of two or more. Studies to determine if such a difference applies to carcinogenesis have not been reported.

Although the "αD" component of the overall dose-response curves appears to be unaffected by dose rate, departures from such invariance (presented in Section 6) can be shown under special laboratory conditions. For example, the slope of the exponential portion of survival curves after high-LET irradiation can be altered by varying such parameters as cell age, nutrient content of the medium, and temperature. Additionally, in bacteria having well-characterized deficiencies in repair mechanisms, it has been shown that the slopes of the curves may differ substantially from that of the wild type. The extent to which observations such as these should be considered in mammalian mutagenesis and carcinogenesis is not known.

Effects on *plants,* for a wide range of endpoints, show in general a dependence of effect on the dose and dose rate. Although the dose-response relationships for plant tumorigenesis are similar to those seen in mammals, dose-rate effects have not been studied. The dose and dose-rate dependence of genetic effects in plants has been well documented.

Cell inactivation seems to have a significant influence on the shape of the dose-response curve for tumorigenesis in general. This is marked at high doses and is seen as a flattening of and even a decrease in the slope of the dose-response curve. Cell inactivation is presumed also to affect the curve at intermediate doses. Hence, studies on cell inactivation and the influence of dose and dose rate are relevant to evaluating tumor dose-response curves.

Studies on *cell transformation in vitro* indicate similarities between the dose-response curves so obtained and dose-response curves for tumorigenesis in the mammal. Although dose-rate studies on cell transformation cannot, in general, be carried on over extended time periods, they do afford the opportunity for detailed dissection of the incidence of effects as a function of cell cycle stage and a number of other possible variables. It is expected that many of the factors involved in cell transformation will be sorted out in the near future by means of these *in vitro* preparations since such quantitative studies,

made possible only relatively recently, are increasing substantially in number. Their precise relevance to mammalian tumorigenesis remains to be determined.

Prenatal irradiation has only limited relevance to the question of dose rate, since generally the "window" of sensitivity is restricted by the gestation period and frequently by periods of relative radiosensitivity and radioresistance in the course of development of the embryo. Because the total time during which the exposure can be effective is fixed and limited, the total dose that can be effective, and, therefore, the degree of effect, must be less as the dose rate is reduced.

Based on the assumption that radiation-induced life span shortening at low and moderate doses is due largely to carcinogenesis, studies on the *effects on life span* contribute appreciably to quantitative knowledge on the influence of dose rate in tumorigenesis. Thus, this endpoint can be regarded as an overall "integrator" that allows quantitative evaluation of the total impact of carcinogenesis in the population, with each malignancy weighted by the amount it contributes to a decrease in life expectancy. Also, the problem of "competing risks" and the resulting difficulty of determining the total yield of tumors of specific types (if an animal develops one tumor and dies, this may prevent the development and detection of other potential tumors that may have been "induced") is ameliorated to a degree.

Tumorigenesis in laboratory animals represents a principal basis for the quantitative dose-magnitude and dose-rate considerations developed in this report. There appears to be no tumor system studied (some 11 or more systems have been studied) that represents a clear-cut exception, i.e., some degree of dose-rate dependence of effect either is highly probable or can be demonstrated in all tumorigenic systems investigated (see Sections 9.1.3 and 9.2.4 for discussion of one sometimes considered to be an exception). This finding indicates that a dose rate effect to some degree appears to be essentially ubiquitous for tumorigenesis, as it is for other radiation effect endpoints studied. Equally important is the fact that the degree of dose-rate dependence, as for other radiation effect endpoints, varies from system to system. It is difficult to determine if the variations reflect differences in the mechanisms of tumorigenesis, variation in the efficiency of common similar mechanisms, or both. Thus, although a DREF appears to exist for each tumor system studied, the magnitude of the factor can differ substantially from system to system.

11.2 Repair

Recovery from or "repair" of biological damage is a general biological phenomenon, i.e., if any potentially toxic agent is administered over a

long period of time as opposed to in a single dose, the amount of the agent that can be tolerated is usually greater and often substantially greater. That is to say, a dose-rate phenomenon is widely known and appreciated to apply generally. However, a wide variety of mechanisms could be involved (e.g., metabolism and/or excretion of the toxic agent, "tolerance," cell proliferation, actual repair of lesions, etc.).

Thus, while the word repair has a general or generic meaning, it also has come to be used in a restricted and specific sense. Repair refers also to the mending or restitution, by biochemical (enzyme) mechanisms, of damage to the DNA molecule inflicted by radiation or other harmful agents. It further refers usually to repair of "subeffective lesions" (e.g., sublethal damage) associated principally with low-LET radiation exposure that in itself is incapable of producing the observable effect of interest. The damage can interact in combination, however, to lead eventually to that biological effect. It is these phenomena of subeffective lesions or damage and repair in its restricted meaning (i.e., the relative rates of buildup and decay (repair) of some form of subeffective damage) which are believed to be ultimately responsible for the curvilinearity of the dose-response curve for low-LET irradiation, the dose-rate dependence under these circumstances, and the essential equivalence of these two related observations.

Although repair has been demonstrated by biochemical and biomolecular means for both UV and ionizing radiations (see Setlow, 1978), its presence is often inferred or assumed by the demonstration of a dose-rate effect (or of fractionated exposures). Hence, a demonstration of a dose-rate effect is presumptive (but not conclusive) evidence that repair is operative.

The ubiquity of the phenomenon of repair, as shown in the present and other reports, is striking for low-LET radiation effects in general. Thus, for a variety of acute and chronic endpoints for a large number of biological systems and species, no clear-cut exception was found among normal eukaryotic systems (i.e., diploid cells with active cytoplasm in plant and animal systems). This was found to be true of carcinogenesis as well. A number of tumor systems in animals have been studied and each showed a dose-rate dependence of effect (note a possible exception, Sections 9.1.3 and 9.2.4).

The degree to which recovery or repair from damage is possible varies from biological system to biological system and the recovery capacity of different cell systems in the same animal can show substantial differences. As an example, the epithelium of the bowel can repair early radiation damage (cell depletion) many times more effectively than can the bone marrow cells. Another example is less repair of genetic damage in irradiated sperm (cells with little active cyto-

plasm) than in irradiated sperm-precursors having a complete complement of cytoplasm.

Of substantial interest and potential importance is the altered (decreased) repair capability in the cells of human beings with genetically-determined biochemical deficiencies, which can be manifested as an increased susceptibility to ultraviolet (UV) and x-ray tumorigenesis (discussed below under "Sensitive Subpopulations").

11.3 Curve Fitting: Data Limitations

Data on low-LET radiation carcinogenesis in human populations are extensive at high doses and dose rates, but still limited at low doses and dose rates. They are adequate to provide reasonable estimates of risk coefficients for high doses and high-dose rates, for a variety of radiation-induced tumors. They are inadequate, however, to allow confident definition of the shape of the overall dose-response curve, especially at low doses. Examples of factors that could bias the interpretation of the human data include: the neutron contribution in Hiroshima; competing influences of destructive forces other than radiation at Hiroshima and Nagasaki; the influence of drug therapy on British patients receiving x-ray therapy for ankylosing spondylitis, or the effects of the disease on subsequent cancer risk; and among other studies: small study sizes and inadequate dosimetry; inadequate comparison populations; inadequate follow-up; inadequate control for other carcinogenic exposures; etc. Thus, while human data are necessary and adequate for the derivation of high-dose and dose-rate risk coefficients, they are inadequate alone for satisfactory evaluation of the shape of dose-response curves at low doses and/or dose rates. The main problem is the requirement of enormously large study sizes to evaluate the risk of low-level exposures.

It is often stated, however, that a set of human data is "consistent with" proportionality. The "consistent with," however, then often becomes equated to the linear, no threshold curve being, in fact, the "best" or only acceptable fit to the data. This emphasis on proportionality is inherent in the purely statistical questions often asked, e.g., "Is a straight line consistent with the data," or "Can the fit be improved by functions other than linear?", as opposed to the more radiobiological question, "Will the limits of error on the data equally well or adequately fit the non-linear curves that might be expected from animal data, i.e., a linear-quadratic or similar function?" A linear function may well adequately represent a set of data, when by simple inspection of the limits of error on the data points, it is obvious that a number of

substantially different curves also could be drawn through the data, within those limits of error.

There are no human data that allow definitive statements with respect to whether a dose-rate influence applies, or does not apply. There are sets of data that have been taken to indicate that there is a dose-rate effect. The same data have also been used to support the claim that there is not a dose-rate effect. The problem is that there are random and systematic errors in the dose, the incidence, or both, that make satisfactory resolution impossible at present. Thus, it is important to determine if generalizations can be established from data other than those that currently exist on the human being.

The apparent shape of dose-response curves for carcinogenesis in different species can be affected markedly by the "saturation phenomena" (slope decreases and may become zero followed by a negative slope). This factor bears directly on judging, with a given set of limited data, the degree to which simple linear interpolation or other functions may represent the slope of the curve at intermediate doses and dose rates. It is sometimes stated that, with scanty data on the human being, linear interpolation might underestimate the risk at low doses because the few data points available might be located either below or above the maximum slope region of the dose-response curve.

It is questionable, however, that serious problems in these regards are experienced in practice. The saturation phenomenon is seen clearly in animal systems, and the dose regions are evident. The data for some tumors do not show saturation. Similarly for man, some tumors do not appear to show this phenomenon, e.g., leukemia. Saturation may be present, however, in other data, e.g., for human female breast cancer (Section 10). This is obvious, however, and indicates that such high-dose data should not be used in the interpolation. Also, in most animal and human systems the curves do not saturate until doses of the order of 300 or more rads of low-LET radiation are reached; and the slope in animal data does not reach zero or become negative until doses of the order of 300 to 400 rads or more are reached. It would thus seem reasonable that, with interpolation of human data from the dose range of 300 to 500 rads, the slope is unlikely to be appreciably biased because of the possibility that the data points might have been in the region of a zero or decreasing slope.

Since one can fit equations to curves for tumorigenesis in animals to accommodate the "cell killing" contribution to the overall curve (see the equations in Figure 3.5), it might then be possible, at least in principle, to subtract this component in an effort to "correct" the slope of the curve in the intermediate dose range for animal and perhaps

for human data (Barendsen, 1978). While the approach is attractive and should be pursued, information is considered to be too limited at present to warrant its application to the human situation. The shape of the dose-response curve may also be affected by "competing risks," a subject that deserves more attention (Groer, 1978).

11.4 Models and Their Uses

The "$\alpha D + \beta D^2$" model is used extensively in this report, partly because it does describe accurately a large amount of data in cellular systems, and because of its simplicity. It embraces well the widely-observed curvilinearity of response and the dose-rate dependence of effect, both of which have a radiobiological basis in repair of subeffect damage at the molecular level (Setlow, 1978), and which appear to be consistent with or are incorporated into a large number of other models (the classical "hit" models; Lea, 1955; Kellerer and Rossi, 1972; Leenhouts and Chadwick, 1978; Burch, 1965; Vanderlaan, 1976; Totter, 1979).

It is emphasized that the "$\alpha D + \beta D^2$" model is utilized, particularly when referring to endpoints in systems more complicated than those involving observations on single cells, as purely a framework for discussion, with no intended implication with respect to mechanisms. Further, the DREF values developed in this report are derived empirically from observations on mutagenesis and carcinogenesis in the mammal, and are not dependent on the validity of the model used or of any other model.

While a linear-quadratic formulation holds well for a number of cellular and subcellular endpoints involving DNA damage, and while DNA damage is generally accepted as being related to mutagenesis and carcinogenesis in the mammal including man, the dose-response curve for the more complicated endpoints may not necessarily conform to this model. For instance, if cancer induction results from multicellular events, then—while the linear quadratic model might hold for an initial event in a single cell—the manifestation of carcinogenesis might be more complicated. Evidence for radiation tumorigenesis being determined by radiation effects on a number of interacting cells has been put forth for one tumor system, the breast tumors in the Sprague-Dawley rat (Rossi and Kellerer, 1972). Also, the single cell (clonal) origin of cancer would not necessarily mean that the response will be "linear quadratic," e.g., preleukemia cells may well exist that require only additional injury to become leukemic. The question of single versus multi-cellular origin of cancer is receiving a large amount of

attention (Buetler *et al.,* 1962; Fialkow *et al.,* 1967, 1977; Gould *et al.,* 1978; Iannacone *et al.,* 1978; Wiggans *et al.,* 1978).

11.5 RBE Considerations

Although relative biological effectiveness (RBE) is not addressed specifically in this report, it does have indirect bearing with respect to the shape of the dose-response curves. Complete dose-response curves have been obtained for both high- and low-LET radiations in a number of biological systems. Essentially without exception in eukaryotic systems, the RBE of high-LET radiation is a strong function of dose, increasing as the dose decreases. It follows from this that at least one of the curves must be non-linear. With one possible exception (see Sections 9.1.3 and 9.2.4 for discussion), the non-linearity in animal systems has been found to be confined almost entirely to the low-LET radiation, at least at low doses. Thus, if it should be concluded, for most tumors resulting from exposure to low-LET radiation, that the response is in fact linear, this would be inconsistent with a very large amount of data on RBE in a large number of systems (see Section 10.2 for an apparent exception in human data, i.e., those for female breast cancer in the Hiroshima-Nagasaki data. Possible explanations, e.g., random and/or systematic uncertainties, are to be discussed in a forthcoming report on LET effects. Such a conclusion of strict linearity for carcinogenesis in general, or even for any specific tumor, would be counter to a large amount of accumulated knowledge with respect to the mechanisms of action of both low-LET and high-LET radiations.

Another important consideration (also to be considered in the forthcoming LET report) is a substantial "RBE" (2 to 3 or greater) between different-energy x and gamma radiations, all within the LET range of the "standard" low-LET radiation referred to in radiation protection (Bond, 1978). This is demonstrable at present only in simple systems. The explanation lies in the fact that at high doses in which the "βD^2" component of low-LET radiation is dominant, the difference between these radiations is the 10 to 15 percent classically reported. At the low doses and dose rates observable only in simple systems, however, and where the "αD" component is dominant, the difference is substantially higher.

11.6 Sensitive Subpopulations

Data on sensitive subpopulations provide at once one of the strongest direct pieces of evidence for the existence and importance of repair (and hence of dose-rate dependence) in radiation carcinogenesis in

man and the identification of (fortunately quite small) groups which apparently are abnormally sensitive to radiogenic cancer.

It is well known that marked differences in sensitivity to radiogenic cancer occur as a function of age and hence sensitive subpopulations do exist on this basis. Claims have been made additionally, on the basis of epidemiological data, that such groups may exist on the basis of other conditions or diseases present (i.e., allergy prone, virus infection of mother while individual was *in utero,* etc.). Such claims have been shown to be unsupported by the data (see Section 11.7 below). Similar claims in animal populations (Oftedahl, 1964c) are equally unconvincing, however, since subgroups of markedly different ages were used for comparison.

Baum (1973) has postulated such subgroups as a possible explanation for the decreasing slope with dose noted in some of the Hiroshima-Nagasaki tumor data. Such an effect may be seen at relatively low doses in the Hiroshima data. Such results are seen at high doses in animal data and have been explained on the basis of "cell killing." This would seem clearly to be the case for high doses of low-LET radiations, and perhaps also for the effect seen at lower doses with high-LET radiations as well. The question will be addressed in the forthcoming report on high-LET effects.

There is definite evidence, however, of individuals who are biochemically repair deficient and for whom there is good evidence for an increased susceptibility to carcinogenesis. In one disease, *Xeroderma pigmentosum,* the individuals cannot repair UV damage effectively (See review, Setlow, 1978) and show a marked (orders of magnitude greater than normal) susceptibility to light-induced cancer, but apparently not to ionizing radiation-induced cancer. In another disease, *Ataxia telangiectasia,* the individuals are sensitive to x rays (see Setlow, 1978; Taylor, 1975), but show no increase in sensitivity to light-induced cancer. This specificity indicates strongly that the repair mechanisms for UV and ionizing radiation are different. It also indicates strongly that repair (and hence dose rate) are important in the human being with respect to both UV and ionizing radiation carcinogenesis.

The incidence and sensitivity differentials of these diseases particularly for ionizing radiation, appear to be so low that even their increased sensitivity to radiation would not be likely to influence detectably the dose-effect response of a large random population containing a normal number of such individuals. Clearly, however, this developing subject area must be followed closely.

11.7 Reports of Excessive Effects at Low Dose

Several reports have been published, some recently, seeming to

indicate degrees of carcinogenic radiation effects at low doses in man that would be incompatible with the linear hypothesis being conservative (and therefore with a DREF being applicable to man). These reports are commented on below:

Human thyroid tumor data (Brown, 1976; Modan *et al.,* 1977) appear to show that the risk coefficients at low doses may be equal to or even greater than those at high doses and dose rates. However, there are substantial uncertainties in dosimetry. Interpretation of the low-dose thyroid cancer effect in the Modan series (Modan *et al.,* 1977) must consider the possibility that (a) imprecise irradiation techniques or restless children could have resulted in direct thyroid exposure; (b) pituitary irradiation may have influenced thyroid cancer risk; (c) there may have been interactions between radiation and other factors such as ethnic, nutritional deficiencies, or goiter to alter the risk. These results must be balanced against the possible influence of pituitary irradiation in these cases, the lack of thyroid tumors in other similar series, and the lack of such an effect in children in Utah who apparently received thyroid doses from fallout radioiodine much larger than those reported in the Modan series (see Section 10.3).

It has been reported (Bross and Natarajan, 1972; Bross and Natarajan, 1977; Bertell, 1977; Bross *et al.,* 1979) that the risk coefficient for tumorigenesis following *in utero* or adult diagnostic x rays is greater than that observed at high doses and dose rates. These reports represent re-analyses of data from the "Tri-state" study of the early 1960s (Graham *et al.,* 1966; Gibson *et al.,* 1972). The "Tri-state" study was a population-based leukemia case-control study. Three hundred and nineteen children with leukemia from upstate New York and the metropolitan and rural areas around Baltimore and Minneapolis-St. Paul were compared with controls drawn from a random sample of children from these areas. For the adults, 1440 adult leukemia cases and 1370 adult controls were evaluated. Exposure histories were ascertained in the cases of leukemia and controls. Thus, the Tri-state study involved the determination of diagnostic x-ray exposures in approximately 1700 persons who developed leukemia during a three-year period compared with the exposure histories in a comparable number of controls. No radiation dosimetry was performed or attempted, and it is extremely difficult to exclude the possibility that some factor that selected people for diagnostic radiation might also be associated with the increased risk of leukemia.

In addition, some of the findings are inconsistent and difficult to explain, e.g., no risk was observed in females; children exposed *in utero* had the same risk as children whose parents received diagnostic x rays prior to conception. Also, the risk appeared concentrated in the few individuals who received inordinately large numbers of diagnostic

examinations, i.e., the risk occurred in those who received large total doses. A re-analysis of the data purporting to show that children with certain "indicator diseases" (viral or bacterial infections and allergy) are associated with radiogenic leukemia was incompatible with the radiogenic basis, but was compatible with the hypothesis that the children with leukemia are more prone to these diseases before the clinical onset of leukemia (Smith *et al.,* 1973). These diseases probably characterize the natural history of leukemia and do not relate to the child's inherent susceptibility to leukemia. Further difficulties in the interpretation of the data are introduced because of the non-standard statistical methods used in the re-analyses (Bross and Natarajan, 1972; Bross and Natarajan, 1977; Bertell, 1977). These methods have subsequently been severely criticized (Smith *et al.,* 1973; Land, 1977; Oppenheim, 1977; Boice and Land, 1979; Rothman, 1977; MacMahon, 1972) as have the conclusions. The present evaluation must concur with that of the original authors (Graham *et al.,* 1966; Gibson *et al.,* 1972) and of the 1972 BEIR Committee (NAS, 1972) that the original results are worthy of note, but that confirmation by independent studies is required and has been encouraged (NAS, 1974).

Mancuso *et al.* (1977) have reported preliminary findings on the work and survival experience of 24,939 male workers with 3,520 certified deaths and of an unspecified number of female workers with 412 certified deaths at the Hanford Works, Richland, Washington between 1943 and 1971. The preliminary report, largely limited to an analysis of data on the 3,520 male deaths for which death certificates were available, claims to demonstrate a radiation-induced excess of cancers. This analysis has been widely criticized (Anderson, 1978; Mole, 1978; Gilbert and Marks, 1979; Hutchison *et al.,* 1979; Reissland, 1978). The report (Mancuso *et al.,* 1977) does not state the actual individual doses received by Hanford workers who died of cancer, only mean cumulative radiation doses. Besides, the study did not take into account the calendar year in which the cancer began and made no correction for the fact that the incidence of cancer in the population at large increased substantially during the period of observation. Additionally, Manuso *et al.* (1977) performed a proportional mortality analysis but excluded information on workers who were alive. Other analyses of the same data by Gilbert and Marks (1979) and by Hutchison *et al.* (1979) point to the possibility of an association with work experience for only two cancer types: cancer of the pancreas and multiple myeloma. There is no suggestion of a radiation relationship for lymphatic or haemopoietic cancers other than myeloma, i.e., no excess of leukemias (which previous experience suggests should have been most observable where radiation is a factor), and no association with lung cancer.

Since the specified radiation doses were very small, perhaps on the order of a few rads, the cancer-doubling dose estimates presented by Mancuso *et al.* (1977) have been strongly disputed. If the postulated small dose actually caused a doubling of the spontaneous rate of cancers, than background radiation would produce more than the numbers of cancers observed in the population (Hutchison *et al.,* 1979). It therefore appears that if the observed risks are real and not artificial something other than radiation was the cause of the observed cancers. The influence of other occupational and nonoccupational carcinogens could not be discounted. Although myeloma has been reported to be in excess among atomic bomb survivors who received doses greater than 100 rads (Ishimaru and Finch, 1979) the relationship is weak and thus would be particularly difficult to see at the low doses involved in the study of Mancuso *et al.* (1977).

Najarian and Colton (1978) estimated that since the Portsmouth Naval Shipyard (PNS) in New England began to service nuclear-powered ships in 1959, 20,000 people were employed there, of whom about 20 percent were exposed to radiation. From a search of death certificates for the period 1959–1977, 1,450 former PNS employees who had died below age 80 were identified in New Hampshire, Maine, and Massachusetts. To ascertain whether these ex-employees were radiation workers, attempts were made to contact near relatives by telephone. This was successful in 525 cases and it was established that 146 were probably exposed to radiation during their working life.

Najarian and Colton (1978) show that, compared with mortality in U.S. white males for 1973, the observed numbers of cancers and leukemias were considerably greater than those expected. For example, 56 cancer deaths were found in death certificates of 146 ex-workers exposed to radiation; only 34.5 were expected. In non-exposed workers, there were 88 cancers; 79.7 were expected. For leukemias, there were 6 in the former radiation workers; only 1.1 expected. This was a preliminary proportional mortality analysis in which expected deaths were based on the proportion of deaths in the United States' white male population and not a mortality analysis based on mortality rates.

Najarian and Colton (1978) listed some inadequacies in their survey. It was an analysis of deaths only; no information was available on the total population at risk. Information supplied by relatives and obtained by newspaper reporters could have been biased. It is also possible that workers merely had a low proportionate mortality from some other cause of death, such as heart disease rather than a high proportional mortality from cancer. No information was available on how long workers had worked at the shipyard, how long nuclear workers were exposed to radiation, and the amounts of radiation they received.

Consideration was not given to other toxic agents, such as asbestos, smoking, or industrial solvents which could have acted alone or synergistically with radiation to cause the apparent excess deaths from cancer and leukemia.

There are other inadequacies in this survey (Hamilton, 1979). To exclude some of the effects of other carcinogens, one must show that cancer frequencies increase with increasing radiation exposure, but knowledge of the lifetime accumulated doses of the former employees was not available. More importantly, if the radiation work at PNS began only in 1959, it is unlikely that changes in overall cancer frequency induced by radiation would be detectable until at least 10 years after exposure, or after about 2 to 5 years for leukemia, to be consistent with the latent periods for cancer induction in most human experience. The data given in Najarian and Colton (1978) can be divided into the periods from 1959–69, when radiation effects would not be apparent, and 1970–77, when effects might be expected (Hamilton, 1979). In 585 death certificates for the period from 1959–1969, 24.6 percent had cancer as the cause of death. Considering the 33 radiation-exposed workers who died during this period, 39.4 percent of the deaths were due to cancer. In 865 death certificates for the period from 1970–1977, 25.7 percent had cancer as the cause of death. Hence, there was no significant difference between the percentage of cancer between the two periods for all workers. For the 113 radiation-exposed workers, 38.1 percent of deaths in the later period were due to cancer—no more than in the earlier period (39.4 percent).

	All deaths	Cancer deaths	% cancer deaths	Radiation exposed		
				All deaths	Cancer deaths	% cancer deaths
1959–69	585	144	24.6	33	13	39.4
1970–77	865	222	25.7	113	43	38.1
	1,450	366				

The absence of any apparent latent period effect casts doubt on conclusions about the contribution of radiation to the curiously high numbers of cancer deaths among the radiation workers (Reissland and Dolphin, 1978). One must await the results of the complete survey being carried out by the Center for Disease Control and the National Institute for Occupational Health and Safety before any conclusions can be drawn between exposure to radiation at PNS and risk of cancer.

An increase in leukemia in children in Utah, resulting presumably from exposure to fallout radiation from weapons testing in Nevada, has been reported (Lyon *et al.,* 1979). No quantitative estimates of dose are available and hence the studies could suggest only a change in disease incidence in selected counties in Utah and could not chal-

lenge current risk coefficients. The authors themselves point out other serious uncertainties in the data. Other problems of interpretation of this correlation study include: (a) Exposure was measured in counties not individuals; (b) It is uncertain whether persons who died in high-fallout counties were actually living there at the time of exposure; (c) The high-fallout counties are rural, with a declining population and the low-fallout counties are urban and growing, and urban-rural differences may have influenced the differences in some manner; (d) In fact, the high-fallout death rate was not high, rather the low-exposure death rate was low; and (e) There was an opposite trend with respect to fallout exposure for other cancers and overall there was no radiation associated with total childhood cancers (Land, 1979).

A preliminary report of 3,224 military personnel, present at an atmospheric test in Nevada called Smoky, suggested an increased risk of leukemia, eight observed cases versus 3.5 expected based on general population incidence rates (CDC, 1979). The mean 1957 cumulative gamma dose for the entire cohort was 493 millirem. Film badge readings were available for seven of the eight leukemia cases and range from 0 to 2997 millirem (mean 1,178 millirem). The interval between the test and leukemia diagnoses ranged from 11 to 19 years (mean 15.6). Interpretation of these results is uncertain at this time for the following reasons: (a) Followup is incomplete and only 60 percent have been located; (b) The study was initiated because of the development of leukemia in a man present at the test, and it is unclear how the study population was identified—it is unlikely that all Smoky participants were identified for study; (c) One of the leukemias was of the hairy cell type. This is believed to be a variant of chronic lymphocytic leukemia, a type of leukemia not known to be induced by radiation; (d) The longer appearance times between exposure and diagnosis of leukemia (mean 15.6 y) are not consistent with other studies of radiogenic leukemia where the risk was greatest four to eight years after exposure; (e) Veterans differ from the general U.S. population because of the selection procedures in force at the time of military induction; (f) The intense case-finding in the test participants likely is much greater than that which occurred in the general population and might account for the apparent leukemia excess; (g) The dose estimates are uncertain and film badges would not have recorded the dose from any ingested or inhaled radionuclides.

It has been claimed (Morgan, 1975) that low-level exposure may in fact be more hazardous per unit of absorbed dose than that at high doses and dose rates. However, in that analysis there was no clear differentiation between effects of high- and low-LET radiation; hence no demonstration that the claim holds for low-LET radiation.

The $\alpha D + \beta D^2$ formulation and values of α/β for cytogenic endpoints

in human cells *in vitro* have been used (Brown, 1976) to conclude that a dose rate factor of 2 or less may apply to radiogenic cancer in the human being, with the additional implication from other data (e.g., Modan *et al.,* 1974, 1977) that the linear hypothesis might not always be conservative. As discussed in Section 4.1, radiation-induced cytogenetic changes *in vivo* or *in vitro* have not been shown to be directly and causally related to radiation-induced carcinogenesis. Also, the values of α and β for cytogenetic endpoints vary substantially from system to system. Thus, while the $\alpha D + \beta D^2$ formulation is quite useful as a model, it is believed that DREF values derived from tumorigenesis in mammals should have more relevance to man than would values derived from simple systems.

Thus, there are some data and claims suggesting that the linear, no-threshold hypothesis may not be conservative and may even underestimate the effects at low doses and dose rates. (There is also a body of data, with varying degrees of statistical and methodological difficulties, that can be interpreted to show no effects at low doses or even a threshold.) While some are deserving of further investigation, the situations individually or collectively are not convincing enough to argue effectively against either the conservatism associated with the linear hypothesis or of the probable existence of DREF values for the human being.

11.8 The Applicability of Plant and Animal Data to Man

Although "simple" cellular systems, e.g., *Tradescantia* chromosome abnormalities in individual cells, were used extensively in this report to show detailed relationships between the effect of dose and dose rate where such detail can be demonstrated, and while these demonstrations of the effect of temporal pattern of dose delivery do bear indirectly on conclusions for man, only data on mutagenesis and tumorigenesis in mammals were used directly in evaluating possible values of DREF. More specifically, the "$\alpha D + \beta D^2$" relationship that describes so well dose- and dose-rate-phenomena in simple cellular systems (see Sections 2–5) was used as only general reference system in terms of which to discuss and evaluate effects in the mammal, including man. This is because the process(es) of carcinogenesis may involve many more factors than those demonstrable in single cell populations (Metalli *et al.,* 1969; Mole, 1975a, 1975b; Yuhas, 1979). If it were to be accepted generally that most cancers originate from a single "transformed" cell, the relationships developed in simple cellular systems might then be considered to be more directly relevant.

On a cellular level, the responses of human cells appear to be identical to those of animal cells, insofar as influence of dose and dose

rate are concerned, for induction of chromosome aberrations, cell killing, and other endpoints. Although the overall radiogenic response of animals and man appears to be similar, the extent to which the mechanisms of induction of different tumors are the same or similar remains to be determined.

Several possible mechanisms of radiogenic cancer in animals are discussed below with respect to their possible bearing on dose-magnitude and dose-rate effects: 1) The cancer origin is purely clonal (origin and development involve a "mutation" in a single radiation-affected stem cell). An $\alpha D + \beta D^2$ relationship would be expected to hold and a DREF would be expected to apply (see section 2). 2) The origin lies in a radiogenic change in single cells, but more than one cell must be so affected for a tumor to result. The dose-response relationship might then be a pure dose-squared function or possibly a function with an exponent greater than 2. 3) There is a clonal origin, but a second physiological (e.g., hormone) factor is required for maximal, or perhaps any, tumor expression. A DREF might then be expected to apply in determining the number of affected target cells. With respect to the hormone component of the overall tumorigenic response, one might then expect that only doses large enough to compromise organ function would interfere. If the effect of the hormone were negative, i.e., cancer expression is normally suppressed by the physiological factor, then only high doses sufficient to impair organ function would be expected to interfere. For a virus etiology, there is evidence that a certain amount of tissue damage may be necessary for the tumor to develop, at least in some cases (Lieberman and Kaplan, 1976). If so, a threshold might be expected to apply.

Hence, for the radiogenic mechanisms of cancer induction in animals referred to above, one might expect that the effect per absorbed dose at low-LET would be reduced as either the dose magnitude or dose rate is reduced. There does not appear to be a demonstrated mechanism for the expectation that the "linear, no threshold hypothesis" would underestimate the effect of low doses and/or dose rates (see Section 11.6 on sensitive subpopulations). Rather, the mechanisms referred to above would lead to the conclusion that the linear, no threshold hypothesis might overestimate the effect per absorbed dose at low doses and dose rates.

A DREF has been accepted for two decades with respect to genetic effects of radiation (NAS, 1972). In fact, since there are available no adequate dose-response data on the genetic effects in man, the absolute risk coefficients to which a DREF is applied have also been developed on the basis of animal data. This, then, is a precedent, widely accepted, for the use of quantitative radiation data derived from animals, to apply to man. It is thus reasonable to evaluate the use of animal data

to establish values of DREF with the expectation that the same may apply to man.

Radiotherapists over the years have also used animal data to aid in evaluating such parameters as the skin erythema dose from different types of radiation delivered at different dose rates. This represents another precedent for the application of animal radiation data, particularly on dose rate, to man.

There is a consistency of findings for dose-magnitude and dose-rate effects for all of the biological endpoints discussed, presumably because of common features in the target, the induced damage, and its repair in various test systems even among different species. So generalized and striking is the dose-rate dependence of effects, including mutagenicity and carcinogenicity, among living species in general and across endpoints, that it would be difficult indeed to make the case that man represents a single exception in this regard. A dose-rate effect for mutagenesis in man has been explicitly assumed for two decades. The demonstration of a single exception for one endpoint (carcinogenesis) for one species (man), particularly when a dose-rate sparing effect is evident in man for a number of endpoints other than carcinogenesis, would be essentially unique in biology and medicine.

With the above facts in mind, one might expect little question with respect to whether a DREF should be applicable to carcinogenesis in man; the only question might be the magnitude of the DREF that should be applied to different tumor systems and to the aggregate of tumors induced by whole body exposure under different circumstances.

Some previous committees (UNSCEAR, 1972) have relied heavily on animal data in concluding that linear interpolation most likely overestimates the degree of effect and thus should not be used for realistic estimation of consequences at low doses and dose rates. The BEIR Committee (NAS, 1972), on the other hand, relied principally on human data and provided estimates only on the basis of linear interpolation without using a DREF. It was concluded in the BEIR Committee that data on human beings were inadequate to show whether or not a DREF should be applied to human data. The decision was made not to rely on animal data for a DREF, and consequently only linear interpolation of human data was used.

Although the influence of dose magnitude and dase rate on the biological response has been recognized in the major reviews and analyses of the extensive radiobiological data available, including those on mutagenesis and carcinogenesis (e.g., NAS, 1972; UNSCEAR, 1972), there appears to have been definitive efforts to quantify these effects in only two previous reports. In the Reactor Safety Study (NRC, 1975) a maximum factor of 5 was introduced (i.e., it was stated that at very low doses and dose rates, the carcinogenic effect of low-LET radiation

would be expected to be 5 times less than that seen at high doses and dose rates). In the more recent UNSCEAR report (1977), a similar factor of about 2.5 was suggested, with the indication that the degree of effect could be larger (see, for example, paragraphs 317 and 318, page 414, and paragraph 27, page 6 of UNSCEAR, 1977).

Values of DREF in this report have been developed on the basis of animal data. Emphasis was placed on whole body exposure and thus on the total tumor response resulting from the simultaneous exposure of all organs. Reliance was also placed on life shortening which, at low doses, is believed to be due largely to the tumorigenic response.

It was considered whether a DREF for carcinogenesis in man could be excluded on the basis of human data. Specific sets of data and arguments that appear to do this were examined critically in the development of this report, and were considered insufficiently compelling to make the case against the application of the DREF factors to man.

12. Summarizing Arguments; DREF Values

In this section a condensed version of the factors and considerations used in the development of dose rate effectiveness factors (DREF) is presented. Because of the paucity of quantitative data from human populations that bear on the relationship between the magnitude and/or temporal distribution of dose and the biological effectiveness of low-LET radiations per unit absorbed dose, relevant data from a large number of biological systems and species have been reviewed and evaluated in this report. Although studies of a wide spectrum of biological endpoints in different experimental systems were included, attention has been principally focused on the hereditary and carcinogenic effects that might be expected to occur in man after exposure to low doses and/or higher doses (up to about 350 rads) delivered at low dose rates. The evaluation has resulted in the following observations and conclusions (reference to dose without specification of dose rate is intended to imply high-dose rate delivery):

a. The initial portion of the dose-response curves for low-LET radiation generally increases in slope with increasing dose for many radiobiological endpoints, including late and genetic effects in a large spectrum of tissue culture, plant, and animal systems, i.e., the effect per unit absorbed dose is an increasing function of the magnitude of the dose; see Curve A, Figure 2.1. For both tumorigenesis and mutagenesis, the response characteristically turns downward as single doses are increased beyond a region of maximum effectiveness in the range of 150–500 rads, apparently due to cell killing.

b. In a large number of systems, the shape of the dose-response curves from the low to high dose ranges may be represented accurately by an equation of the form

$$I = \alpha D + \beta D^2, \tag{12.1}$$

in which I is the incidence of effect, D is the absorbed dose, and the coefficients α and β are constants. This relationship and the model it implies is used as a basis of discussion throughout the report. However, this does not necessarily imply a belief that the

model corresponds directly to the detailed mechanisms involved in the production of the diverse biological endpoints discussed.

c. It follows that linear interpolation between the naturally occurring spontaneous incidence in a population at zero or background dose and the total incidence observed in this population when exposed to high doses (or total, corrected for spontaneous incidence; see Curve B, Figure 2.1) (referred to henceforth as the "linear hypothesis") generally over-estimates the degree of effect per unit absorbed dose at low doses. The accurate establishment of the extent of this overestimation, as the dose magnitude is reduced, becomes difficult or impossible in most biological systems due to the large number of observations and/or subjects that are required to obtain statistical confidence.

d. In addition, the effect per unit dose of low-LET radiation for the induction of cell killing, chromosome aberrations, mutations, teratogenic effects, shortening of life, and tumor formation in experimental systems has been consistently observed to depend upon the temporal distribution of dose. In essentially all endpoints that have been examined, from cell death to tumor induction, a reduction in dose rate diminishes the degree of biological effect per unit dose (e.g., contrast Curve C with the high dose region of Curve A, Figure 2.1). In lower systems, in which suitable numbers may be observed to provide adequate quantification as the dose rate is decreased, the lower limit of diminished effect per unit absorbed dose is found not to be zero. Rather, it is the straight line Curve D (Curve C becomes superimposed on Curve D), having a slope approximating or equal to α in Equation (12.1) and implying the lack of a threshold. Similar relationships are apparent in experimental tumor systems. At low dose rates data comparable to those for high doses and dose rates represented by the solid circles on Curve A in Figure 2.1 are found to lie on a curve such as C in Figure 2.1. Due to statistical limitations, it is not possible to say if the Curve C in these mammalian systems is actually superimposed on Curve D. It is evident that the words "threshold" and "no threshold effect," particularly in the context of mutagenesis and tumorigenesis, refer to the appearance of the effect or endpoint of interest in one or a few individual(s) in an (usually large) exposed population, or alternatively to the probability or "risk" of that endpoint appearing in an individual in a similar population so exposed.

e. Thus, estimates of effect per unit absorbed dose which are based on the linear hypothesis also overestimate the true effect of high doses that are delivered at low-dose rates. It is possible to obtain satisfactory estimates of the extent of this overestimation for

many endpoints, including mutagenesis and carcinogenesis in many systems. Such estimates are referred to as Dose Rate Effectiveness Factors, or DREF, and in Figure 2.1 the DREF is equal to slope α_L/α_{Ex}.

f. As can be shown in lower systems, the slope of the limiting straight line for low dose rate (Curve D, slope α_1, Figure 2.1) also approximates or equals the initial slope of the lower end (slope α_1) of the full dose-response curve as determined at high-dose rates (Curve A). Thus, in simple systems, an estimate of the DREF as determined experimentally by delivering high doses at high-vs. low-dose rates (i.e., α_L/α_{Ex}) also provides an estimate of the degree to which the linear hypothesis overestimates the effect per unit absorbed dose at low doses (α_L/α_1). The latter cannot usually be determined experimentally. The further implication is that per unit of absorbed dose, the effect of low doses (slope α_1), is the same at high- or low-dose rates, i.e., it may be independent of dose rate.

g. Data on mammalian tumorigenesis and mutagenesis are not inconsistent with the relationships discussed in the preceding paragraph. However, due to statistical limitations it is impracticable to demonstrate the conformity of mammalian systems to the functional relationships that can be shown to apply in simpler systems (i.e., whether or not, as the dose rate for high-dose exposure is reduced, the lower limit does in fact become Curve D, with a slope α'_1 equal to the slope α_1 of the initial part of Curve A). However, the implication is strong that some of these systems may conform. In some experimental tumor systems the slope of the low-dose rate curve can be observed, at doses of 50 rads or lower, to remain below the high-dose-rate curve. It would not be anticipated that the slope would change (particularly that it would become steeper) at still lower doses.

   Thus, the term DREF is used to indicate either dose or dose rate reduction. It is preferable to the term "dose magnitude effectiveness factor" since it has a foundation in data obtained in mammalian systems.

h. The apparent equivalence of the dependence of effect on dose magnitude and on dose rate is not surprising, since both must depend on the same basic phenomenon, i.e., the relative rates of buildup and of decay (or repair) of some form of damage or lesions which must interact in combination to eventually produce the observable biological effect of interest. The result (the net amount of persistent lesion interaction and thus of apparent effect) is thus critically dependent not only upon the dose mag-

nitude, but also upon the temporal pattern of dose delivery. The expectation of a dose rate dependence has a firm basis in known biomolecular mechanisms of repair of DNA damage and would be expected from most biophysical models of radiation effects at the cellular level. The demonstration that cellular repair deficiencies are associated with increased susceptibility to cancer normally and as a result of exposure to chemical and UV or ionizing radiation (Section 11.6) indicates that dose magnitude and dose rate are important in the induction process.

i. Although extensive data acquired from observations of human beings who have been exposed to high doses of radiation permit reasonable risk assessments for tumorigenesis, the amount of data available at intermediate and low doses is inadequate for a conclusive demonstration of the shape of the full dose-response curve. In addition, there are insufficient data pertinent to the dose-rate dependence of tumorigenesis in man to allow confident judgments about any resultant diminution in health risks. No dose-response curves for genetic effects of radiation in man are available. Hence, exclusive reliance has been and must be placed on animal data. The cumulative experimental evidence in plant, animal, and cellular systems may be similarly brought to bear in a formulation of judgments on tumorigenesis in man. Extensive experimental evidence supports the existence of dose magnitude and of dose-rate effects generally, and specifically for mutagenesis and for carcinogenesis in many species of plants and animals. It would be most extraordinary if such dependence were not applicable to the same endpoints in the human being. With these considerations in mind, and since no human data were found that definitely precluded the existence of variable dose magnitude and dose-rate effects in man, it is concluded that they should be assumed to apply to carcinogenesis in the human being (as they have for many years been assumed to apply for mutagenesis). Thus, although many biological systems and endpoints were examined to establish the generality of dose magnitude and dose rate effects, and to develop a model for discussion purposes, empirical ratios derived from mammalian mutagenesis and carcinogenesis are used to develop DREF values, with the expectation that similar values should exist for man. Hence, the values presented are dependent on neither data in lower (non-mammalian) systems nor on the applicability of any model.

j. Since a complexity and a wide spectrum of tumorigenic responses to radiation is found in the experimental animal, and since the detailed mechanisms of such responses in animals or man are not

well understood, the NCRP is reluctant to provide definite quantitative DREF values either for individual tumor types or for all tumors collectively that might be expected in man. For a single exposure to low absorbed doses (between 0 and 20 rads) delivered at any dose rate, and for any total dose delivered at a dose rate of 5 rads y^{-1} or less, it is believed that the DREFs for both mutagenesis and for collective tumors after exposure of the whole body to low dose or dose rate radiation, are likely to be between 2 and 10. The data are considered insufficient to warrant attempts to provide a finer breakdown of DREF values either for exposure by ranges of single doses or for dose rates other than those stated.

k. It follows from the indicated range of DREF values that if the linear hypothesis is applied to data on radiation effects observed in human beings obtained at high doses and dose rates, the resultant risk coefficient would be expected to overestimate the most realistic or correct value, for either single exposure to low doses or exposure to high doses delivered at low-dose rates, by a factor of between 2 and 10.

The extensive evaluations with respect to radiation risk coefficients in this report are focused on, and largely limited to, the effect of dose magnitude and of dose rate. Although not in detail, they address other specific uncertainties (e.g., "plateau" length, relative versus absolute risk) that must also be dealt with in estimating risk coefficients, be they derived from the linear hypothesis or otherwise. It is emphasized that the conclusions on the effect of dose magnitude and dose rate apply only to low-LET radiations.

Appendix A. Definition of Terms

Dose Ranges: Arbitrarily-designated ranges of dose-response curves, such as Curve A in Figure 2.1.

Low Dose. The straight or essentially straight, very low dose portion of the low-LET dose-response curve. For many endpoints, the dose range is roughly 0 to 20 rads. (In *Tradescantia* and for life shortening in mice, 20 rads is the dose at which significant deviations from the linear term can be detected.)

Intermediate Dose. The portion of the curve with increasing slope, between the low dose range and the region of maximum slope (between about 20 and 250 rads, depending on the biological system).

High Dose. From the region of maximum slope to where the slope becomes zero (about 250 to 400 rads, depending on the system).

Very-High Dose. The remaining curve beyond the high dose region.

Dose-Rate Ranges: Arbitrarily-defined ranges of average dose rate are as follows:

Low Average Dose Rate is equal to or below the range that would be expected to yield risk coefficients approximating alpha in the formulation $I = \alpha D + \beta D^2$ in systems in which this model applies. In most systems this certainly should apply at dose rates of the order of 5 rads per year or less, a rate that includes those for background radiation exposure, and radiation protection guides for workers and for the general public.

High Average Dose Rate. A dose rate that would give the maximum, or near the maximum risk coefficients, of high dose rates. In most systems, this would correspond to a total dose of about 200–250 rads, delivered over minutes to about one-half day.

Intermediate Average Dose Rates. Any rate in between low and high dose rates.

Dose Rate Effectiveness Factor: (DREF) The factor by which linear interpolation from data obtained at high doses and dose rates overestimates the risk per unit absorbed dose of radiation delivered at very low doses and/or dose rates. Using the $\alpha D + \beta D^2$ formulation, at a given dose it is $(\alpha D + \beta D^2)/\alpha D$.

Stochastic: "Stochastic" effects are those for which the probability of an effect occurring, rather than its severity, is regarded as a function of dose, without threshold. "Non-stochastic" effects are those for which the severity of the effect varies with the dose, and for which a threshold may therefore occur.

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1. Collect, analyze, develop, and disseminate in the public interest information and recommendations about (a) protection against radiation and (b) radiation measurements, quantities, and units, particularly those concerned with radiation protection;
2. Provide a means by which organizations concerned with the scientific and related aspects of radiation protection and of radiation quantities, units, and measurements may cooperate for effective utilization of their combined resources, and to stimulate the work of such organizations;
3. Develop basic concepts about radiation quantities, units, and measurements, about the application of these concepts, and about radiation protection;
4. Cooperate with the International Commission on Radiological Protection, the International Commission on Radiation Units and Measurements, and other national and international organizations, governmental and private, concerned with radiation quantities, units, and measurements and with radiation protection.

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The Council is made up of the members and the participants who serve on the sixty-nine Scientific Committees of the Council. The Scientific Committees, composed of experts having detailed knowledge and competence in the particular area of the Committee's interest, draft proposed recommendations. These are then submitted to the full membership of the Council for careful review and approval before being published.

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SC-52:	Conceptual Basis of Calculations of Dose Distributions
SC-53:	Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Radiation
SC-54:	Bioassay for Assessment of Control of Intake of Radionuclides
SC-55:	Experimental Verification of Internal Dosimetry Calculations
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The Council's activities are made possible by the voluntary contribution of time and effort of its members and participants and the generous support of the following organizations:

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To all these organizations the Council expresses its profound appreciation for their support.

Initial funds for publication of NCRP reports were provided by a grant from the James Picker Foundation and for this the Council wishes to express its deep appreciation.

The NCRP seeks to promulgate information and recommendations based on leading scientific judgment on matters of radiation protection and measurement and to foster cooperation among organizations concerned with these matters. These efforts are intended to serve the public interest and the Council welcomes comments and suggestions on its reports or activities from those interested in its work.

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Lauriston S. Taylor Lectures

No.	Title and Author
1	*The Squares of the Natural Numbers in Radiation Protection* by Herbert M. Parker
2	*Why be Quantitative About Radiation Risk Estimates?* by Sir Edward Pochin
3	*Radiation Protection—Concepts and Trade Offs* by Hymer L. Friedell

NCRP Reports

No.	Title
8	*Control and Removal of Radioactive Contamination in Laboratories* (1951)
9	*Recommendations for Waste Disposal of Phosphorus-32 and Iodine-131 for Medical Users* (1951)
12	*Recommendations for the Disposal of Carbon-14 Wastes* (1953)
16	*Radioactive Waste Disposal in the Ocean* (1954)
22	*Maximum Permissible Body Burdens and Maximum Permissible Concentrations of Radionuclides in Air and in Water for Occupational Exposure* (1959) [Includes Addendum 1 issued in August 1963]

23 *Measurement of Neutron Flux and Spectra for Physical and Biological Applications* (1960)
25 *Measurement of Absorbed Dose of Neutrons and of Mixtures of Neutrons and Gamma Rays* (1961)
27 *Stopping Powers for Use with Cavity Chambers* (1961)
30 *Safe Handling of Radioactive Materials* (1964)
32 *Radiation Protection in Educational Institutions* (1966)
33 *Medical X-Ray and Gamma-Ray Protection for Energies Up to 10 MeV—Equipment Design and Use* (1968)
35 *Dental X-Ray Protection* (1970)
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37 *Precautions in the Management of Patients Who Have Received Therapeutic Amounts of Radionuclides* (1970)
38 *Protection against Neutron Radiation* (1971)
39 *Basic Radiation Protection Criteria* (1971)
40 *Protection Against Radiation From Brachytherapy Sources* (1972)
41 *Specification of Gamma-Ray Brachytherapy Sources* (1974)
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50 *Environmental Radiation Measurements* (1976)
51 *Radiation Protection Design Guidelines for 0.1–100 MeV Particle Accelerator Facilities* (1977)
52 *Cesium-137 From the Environment to Man: Metabolism and Dose* (1977)
53 *Review of NCRP Radiation Dose Limit for Embryo and Fetus in Occupationally-Exposed Women* (1977)
54 *Medical Radiation Exposure of Pregnant and Potentially Pregnant Women* (1977)

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61 *Radiation Safety Training Criteria for Industrial Radiography* (1978)
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1	*X-Ray Protection* (1931). [Superseded by NCRP Report No. 3]
2	*Radium Protection* (1934). [Superseded by NCRP Report No. 4]

3 *X-Ray Protection* (1936). [Superseded by NCRP Report No. 6]

4 *Radium Protection* (1938). [Superseded by NCRP Report No. 13]

5 *Safe Handling of Radioactive Luminous Compounds* (1941). [Out of Print]

6 *Medical X-Ray Protection up to Two Million Volts* (1949). [Superseded by NCRP Report No. 18]

7 *Safe Handling of Radioactive Isotopes* (1949). [Superseded by NCRP Report No. 30]

10 *Radiological Monitoring Methods and Instruments* (1952). [Superseded by NCRP Report No. 57]

11 *Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water* (1953). [Superseded by NCRP Report No. 22]

13 *Protection Against Radiations from Radium, Cobalt-60 and Cesium-137* (1954). [Superseded by NCRP Report No. 24]

14 *Protection Against Betatron—Synchrotron Radiations Up to 100 Million Electron Volts* (1954). [Superseded by NCRP Report No. 51]

15 *Safe Handling of Cadavers Containing Radioactive Isotopes* (1953). [Superseded by NCRP Report No. 21]

17 *Permissible Dose from External Sources of Ionizing Radiation* (1954) including *Maximum Permissible Exposure to Man, Addendum to National Bureau of Standards Handbook 59* (1958). [Superseded by NCRP Report No. 39]

18 *X-Ray Protection* (1955). [Superseded by NCRP Report No. 26]

19 *Regulation of Radiation Exposure by Legislative Means* (1955). [Out of print]

20 *Protection Against Neutron Radiation Up to 30 Million Electron Volts* (1957). [Superseded by NCRP Report No. 38]

21 *Safe Handling of Bodies Containing Radioactive Isotopes* (1958). [Superseded by NCRP Report No. 37]

24 *Protection Against Radiations from Sealed Gamma Sources* (1960). [Superseded by NCRP Report Nos. 33, 34, and 40]

26 *Medical X-Ray Protection Up to Three Million Volts* (1961). [Superseded by NCRP Report Nos. 33, 34, 35, and 36]

28 *A Manual of Radioactivity Procedures* (1961). [Superseded by NCRP Report No. 58]

29 *Exposure to Radiation in an Emergency* (1962). [Superseded by NCRP Report No. 42]

31 *Shielding for High Energy Electron Accelerator Installations* (1964). [Superseded by NCRP Report No. 51]

34 *Medical X-Ray and Gamma-Ray Protection for Energies Up to 10 MeV—Structural Shielding Design and Evaluation* (1970). [Superseded by NCRP Report No. 49]

Statements

The following statements of the NCRP were published outside of the NCRP Report series:

"Blood Counts, Statement of the National Committee on Radiation Protection," Radiology **63,** 428 (1954)

"Statements on Maximum Permissible Dose from Television Receivers and Maximum Permissible Dose to the Skin of the Whole Body," Am. J. Roentgenol., Radium Ther. and Nucl. Med. **84,** 152 (1960) and Radiology **75,** 122 (1960)

X-Ray Protection Standards for Home Television Receivers, Interum Statement of the National Council on Radiation Protection and Measurements (National Council on Radiation Protection and Measurements, Washington, 1968)

Specification of Units of Natural Uranium and Natural Thorium (National Council on Radiation Protection and Measurements, Washington, 1973)

Copies of the statements published in journals may be consulted in libraries. A limited number of copies of the last two statements listed above are available for distribution by NCRP Publications.

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